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Prevalence, Incremental Cost and Resource Utilization Associated with Opioid Overdoses

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PREVALENCE, INCREMENTAL COST AND RESOURCE UTILIZATION ASSOCIATED
WITH OPIOID OVERDOSES

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of
Philosophy at Virginia Commonwealth University.

by

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LIST OF ABBREVIATIONS

ASD:	Absolute Standardized Difference
ASI-MV®:	Addiction Severity Index Multimedia Version Connect
BRFSS:	Behavioral Risk Factor Surveillance System
CDC:	Centers for Disease Control and Prevention
CCI:	Charlson Comorbidity Index
CI:	Confidence Interval
CR:	Controlled Release
CSD:	Controlled Substance Database
DSM:	Diagnostic and Statistical Manual of Mental Disorders
DAWN:	Drug Abuse Warning Network
ER:	Emergency Room
ER:	Extended Release
XR:	Extended Release
GPI:	Generic Product Identifier
GAO:	Government Accountability Office
HCUP:	Healthcare Cost and Utilization Project
IDU:	Injection Drug User
ICD:	International Classification of Diseases
MEPS	Medical Expenditure Panel Survey
MEDD:	Morphine Equivalent Daily Dose
MME:	Morphine Milligram Equivalent

NAMCS:	National Ambulatory Medical Care Survey
NDC:	National Drug Code
NHAMCS:	National Hospital Ambulatory Medical Care Survey
NIS:	National Inpatient Sample
NIDA:	National Institute of Drug Abuse
NPDS:	National Poison Data System
NSDUH:	National Survey on Drug Use and Health
NVSS:	National Vital Statistics System
NEDS:	Nationwide Emergency Department Sample
NC:	North Carolina
OME:	Office of the Medical Examiner
OTP:	Opiate Treatment Programs
PCC:	Poison Control Center
PMP:	Prescription Monitoring Program
PSM:	Propensity Score Matching
RADARS:	Researched Abuse, Diversion and Addiction-Related Surveillance
SEDD:	State Emergency Department Database
SID:	State Inpatient Database
TNCSMP:	Tennessee Controlled Substances Monitoring Program
TJC:	The Joint Commission
UDOH:	Utah Department of Health
WA:	Washington State

Abstract

PREVALENCE, INCREMENTAL COST AND RESOURCE UTILIZATION ASSOCIATED
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By Batul S. Electricwala, BPharm, PhD Candidate

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of
Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2016.

Advisor: Norman V. Carroll, Professor, Department of Pharmacotherapy and Outcomes Science

Background –

An increase in opioid prescribing has led to an increase in opioid overdoses.[1,2] No study has

estimated the incremental costs subsequent to an opioid overdose event in prescription opioid

users, or the prevalence and costs of overdose events in family members of prescription opioid users and in overdose victims with no identifiable source of prescription opioid. The latter group will be referred to as "others".

Objectives –

The first objective of this study was to estimate the prevalence of opioid overdoses in aforementioned groups. The second objective was to estimate the incremental costs and resource utilization associated with opioid overdoses in these groups.

Methods –

This study is a retrospective analysis using claims data from SelectHealth, a not-for-profit health insurance organization in Utah and southern Idaho. We estimated the prevalence of opioid overdoses in the sample population, as well as in each group, by year. For the cost estimation we collapsed family members and others into one category – "non-medical users". To estimate costs we used an incremental cost approach whereby we used propensity scores to match cases (patients who suffered from an opioid overdose) to appropriate controls (patients who did not suffer from an opioid overdose) and estimated the direct medical costs incurred in each group in the year following an overdose. Generalized Linear Models were used to estimate incremental costs and resource utilization. Sensitivity analyses were conducted to measure the robustness of the estimates.

Results –

The prevalence of opioid overdoses increased by 84.8% in prescription opioid users (from 55.6 per 100,000 in 2011 to 102.8 per 100,000 in 2014), increased by 37.9% in family members of

prescription opioid users (from 5.9 per 100,000 in 2011 to 8.2 per 100,000 in 2014) and increased by 179.9% in others (from 8.2 per 100,000 in 2011 to 23.1 per 100,000 in 2014).

The prevalence of opioid overdoses in acute users increased by 14.7% (from 43.8 per 100,000 in 2011 to 50.3 per 100,000 in 2014) as compared to 165.9% in chronic users (from 187.0 per 100,000 in 2011 to 497.3 per 100,000 in 2014).

The incremental direct medical costs per patient per year were estimated to be $65,277 (p-value<0.05) in prescription opioid users who suffered from an overdose and $41,102 (p-value<0.05) in non-medical users who suffered from an overdose. Overdose-specific costs were estimated to be $12,111 for prescription opioid users and $11,070 in non-users.

Conclusions –

Our study found that the prevalence of opioid overdoses increased steadily from 2011 to 2014 in the sample population. The prevalence of overdoses was much higher in chronic opioid users as compared to acute users. Differences between overdose-specific costs and total incremental costs may suggest that overdoses are associated with substantial costs in addition to costs for the initial treatment of the overdose. While the cost to payers due to overdoses in prescription opioid users is substantial, payers also incur costs from diversion of opioids.

CHAPTER I:

Introduction

Since 2000, the United States has witnessed a 200% increase in the rate of overdose deaths involving opioids.[2] The rise in the number of deaths has been synchronous with the increase in the number of opioid prescriptions– health care providers wrote 259 million prescriptions for opioid analgesics in 2012, enough for every American adult to have a bottle of pills.[3] Increases in opioid prescribing have been accompanied by increases in opioid-related emergency room (ER) visits, inpatient visits, mortality and costs.

Previous studies have estimated costs associated with ER visits and inpatient visits in patients suffering from an overdose event. A study has also quantified the economic burden of opioid overdoses in the United States and estimated costs associated with each episode of poisoning.[4] With this study, in addition to estimating the prevalence of opioid overdose we have addressed several gaps in literature. These include estimating the prevalence of opioid overdoses by acute and chronic opioid use, estimating the prevalence by medical and non-medical opioid use and estimating the downstream costs for patients who suffer from an opioid poisoning event. We used a matched control methodology to compare the healthcare expenditures between the cases (individuals who suffer from an overdose) and controls (individuals who do not suffer from an overdose) after adjusting for comorbidities and other risk factors.

The specific aims, introduction, and background are provided in this chapter.

Chapter 2 provides a literature review regarding previous studies that have estimated the prevalence, source of opioid and costs of opioid overdoses. Chapter 2 also provides the rationale for the study. Chapters 3 explains the methods and results for Specific Aim I and Chapter IV explains the methods and results for Specific Aim II. Finally, Chapter 5 contains the discussion of the results of this study.

Specific Aims

Specific Aim 1 –

A: Estimate the prevalence of opioid overdoses in the sample population

B: Estimate the prevalence of opioid overdoses in prescription opioid users, family members of prescription opioid users and others

B: Estimate the prevalence of opioid overdoses for acute and chronic opioid users

Specific Aim II –

A: Estimate the incremental downstream costs and resource utilization in prescription opioid users who suffered from an overdose

B: Estimate the incremental downstream cost and resource utilization in family members of prescription opioid users and others (non-users) who suffered from an overdose

Background

Poisoning is the leading cause of injury death in the United States. A majority of poisoning deaths are cause by drug overdoses. [5] Each day 46 people in the United States die from an overdose of prescription opioid analgesics. [3] Opioid analgesics are a class of drugs used in the treatment of pain, but they have a high potential for addiction, abuse and misuse.

Opioids

Opioids exert their pain alleviating action by binding at receptors on cell membranes in the central nervous system, intestines and musculoskeletal tissues. The primary receptors identified in humans are mu, delta and kappa. [6] Based on the efficacy and potency at these receptors, opioids are classified as full agonists, partial agonists or agonist-antagonists. Examples of pure agonists are morphine, codeine, hydrocodone, fentanyl and oxycodone. Buprenorphine is a partial agonist; butorphanol and dezocine are examples of mixed agonist-antagonists. Naloxone and naltrexone are pure antagonists and are administered for prevention or reversal of opioid effects. [7]

Opioids are used to treat both acute and chronic pain. Acute pain is believed to be a result of disease, inflammation or injury to the tissue. This pain is usually limited to a shorter time period. An example of acute pain is pain resulting from trauma or surgery. Chronic pain persists over a longer period of time as compared to acute pain and is resistant to most medical treatments. Examples of chronic pain patients are those suffering from cancer or chronic conditions like arthritis. [8] The pain that cancer patients suffer is very different when compared to other chronic

pain and therefore, chronic pain is often further classified as chronic cancer pain and chronic non-cancer pain.

Chronic pain affects an estimated 100 million Americans, or one third of the U.S. population. [9] In spite of lacking evidence for maintenance of pain relief for chronic pain, prescriptions of opioid medications for chronic pain have increased dramatically since the 1990s. [10-13] Among patients starting long-term opioid therapy for chronic non-cancer pain, back pain and extremity pain are the most common pain diagnoses (38% and 30%, respectively).[14]

Nearly 14.5 million Americans with a history of cancer are alive and the number is expected to rise to 19 million by 2024. [15] Approximately one-third of cancer patients report their pain to be moderate to severe. [16] Opioids analgesics are considered to be first line treatment for moderate to severe cancer pain. [17,18]

Opioid epidemic

There were many factors in the 1990s that lead to what is called the 'opioid epidemic' in the United States. The undertreatment of pain was an important issue that was gaining momentum. In the 1980s, pain specialists unequivocally supported the use of prescription opioid analgesics for the management of chronic nonmalignant pain. [19-21] In 1998, the Federation of State Medical Boards in the United States laid out guidelines for use of controlled substances for treatment of pain. These guidelines stated that no disciplinary action would be taken against practitioners based solely on the frequency and/or quantity of opioids prescribed. [22] In 2000, The Joint Commission (TJC) (formerly known as The Joint Commission on Accreditation of Healthcare Organizations) advocated for pain to be recognized as the fifth vital sign in addition to blood

pressure, temperature, respiratory and heart rate. [23] While all these events were in motion, new formulations of opioids were released and there was an explosion of opioids in the market.

As a result of these events, prescriptions for opioid analgesics in the United States increased by 700% between 1997 and 2007. [1] This trend of increased prescribing of opioids has been accompanied by increased levels of prescription opioid overdose. Between 1999 and 2008, the number of drug overdose deaths involving opioid analgesics in the United States saw a three-fold increase. [5] Between 1999 and 2002, deaths attributable to opioid analgesics increased by 91.2%, while those attributable to heroin and cocaine increased by 12.4% and 22.8% respectively. [24]

<u>Clinical manifestations of opioid overdose</u>

Opioid overdose (or opioid poisoning) is characterized by symptoms such as respiratory depression, decreased mental status, miotic pupils and absent bowel sounds. [25] The presentation of overdose can range from euphoria to coma. A complete list of symptoms is given in Table 1. However, the best predictor of opioid overdose is respiratory depression and it can be fatal if left untreated. [26,27]

Table 1 – Clinical manifestations of opioid overdose [28]

---

 1. Respiratory depression

 2. Miosis

 3. Stupor

 4. Hepatic injury from acetaminophen or hypoxemia

 5. Myoglobulinuric renal failure

---

6. Rhabdomyolysis

7. Absent or hypoactive bowel sounds

8. Compartment syndrome

9. Hypothermia

In cases of respiratory depression that lead to fatal overdose, the victim's breathing slows to the point where oxygen levels in the blood fall below the level needed to transfer oxygen to the vital organs. The individual becomes unresponsive, blood pressure progressively decreases and the heart rate slows, ultimately resulting in a cardiac arrest. Death can occur within minutes of opioid ingestion. Often, there is a longer period of unresponsiveness that can last for several hours before the patient dies. This period is sometimes associated with loud snoring, leading to the term "unrousable snorers".[29]

Most cases of opioid overdoses can be managed in the emergency department, with more severe or complicated cases requiring inpatient admission. Pharmacologic treatment for overdoses consists of naloxone, a competitive mu receptor opioid antagonist that reverses the CNS depressant effects of the opioid.[28] It is usually administered in the hospital setting, but can be administered by emergency medical service personnel and now, family members. By June 2016, all but 3 states (Kansas, Minnesota and Wyoming) had passed legislation to improve access to naloxone. These laws are structured into three broad domains which intend to increase naloxone prescribing and distribution, increase pharmacy naloxone access and encourage overdose witnesses to call on emergency responders. However, these laws exhibit heterogeneity across states and differ based on who can receive prescriptions for naloxone, whether laypeople are

allowed to adminsiter the medication and whether the prescribers, dispenser or individuals who administer naloxone are subject to immunity. [30]

<u>Risk factors</u>

Opioid overdose can occur for a variety of reasons. For one, new users of opioid therapy might not be aware of the side effects of their medication and may miss the warning signs of an impending overdose. Patients might experience an overdose event when they switch from one opioid to another as well. [25]

Various studies have examined risk factors for opioid overdose. Patients at an increased risk of opioid overdose are those using higher doses of prescribed opioids, [14,31] long-acting opioids versus short-acting opioids, [32] opioids in combination with other sedating substances, such as alcohol and benzodiazepines, the household members of people in possession of opioids, [33] Medicaid and low-income patients, [34] patients living in rural communities versus urban areas [35], patients with a mental illness, patients with a history of alcohol and substance abuse, [36] patients with a history of opioid dependence and patients with a hospitalization during 6 months before the serious toxicity or overdose event. [37]

Despite the fact that patients who have suffered from an opioid overdose are at a higher risk of suffering from a subsequent overdose, the vast majority of these patients continue to receive opioids. [38]

Two special populations, children and older adults, are at increased risk of overdose.

Overdose in children is characterized by a delayed onset of toxicity, unexpectedly severe overdose and prolonged toxic effects. [39,40] These effects are due to differences in rates of absorption, distribution and metabolism in children as compared to adults. [41] Older adults also have increased susceptibility to opioids and should be monitored closely. This population has various other co-existing conditions and age related changes in physiology and body composition that may increase the risk of an overdose event. [42,43]

Misuse and Abuse

Various terms are used to describe the context under which opioid overdoses may occur.

Misuse and abuse are terms often used to describe behaviors related to opioid use disorders. There are different sets of definitions used for these terms. These are summarized in Figure 1.
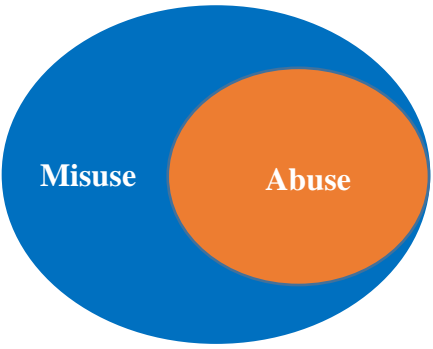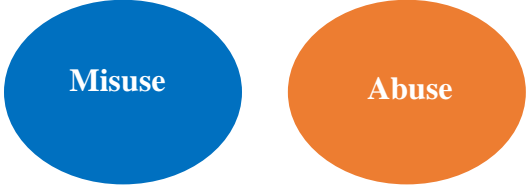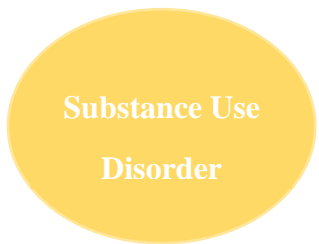
The National Institute of Drug Abuse (NIDA) definitions of misuse and abuse define misuse as an umbrella term for abuse. The differentiation of misuse or abuse is based on whether it is acceptable to use that medication the way it is being used. [44]

NIDA also had a definition specifically for prescription drug abuse – "the use of a medication without a prescription, in a way other than as prescribed, or for the experience or feelings elicited." [45] This definition includes the reason for the abuse.

Katz et al. attribute misuse to medications and abuse to illicit drugs only. This is a more restrictive definition and may not be applicable in the area of opioid analgesics. [46]

In Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), abuse and dependence were collapsed and are now defined as a broad term – substance use disorder.

We will use the NIDA definition of prescription drug abuse in this study.

Definition Source	Definition
NIDA	Misuse – "Taking a medication in a manner other than that prescribed or for a different condition than that for which the medication is prescribed." Abuse – "The intentional misuse of a medication outside of the normally accepted standards of use."[44]
Katz et al.	Misuse – "Use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not." Abuse - "Any use of an illegal drug" or "the intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness."
DSM-V	Substance Use Disorder – "the recurrent use of alcohol and/or drugs causes clinically and functionally significant impairment, such as health problems, disability, and failure to meet major responsibilities at work, school, or home."[48]

NIDA – National Institute of Drug Abuse; DSM – Diagnostic Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)

Figure 1 – Misuse, abuse and dependence definitions (adapted)[47]

Drug Diversion

Diversion of prescription opioids is a widespread problem and can lead to prescription opioid abuse. Diversion has taken many forms: doctor shopping, pill brokering, and, most commonly, taking medications from the family medicine chest. Doctor shopping involves obtaining medications from multiple providers. Pill brokers are agents who partner with Medicare patients to gain access to their pills. There is growing evidence of these practices and alliances between

healthcare providers and patients for diverting and selling prescription opioids. [49–51] A study among Medicare patients revealed that 12% of Medicare patients filled prescriptions from 4 or more opioid providers. [52]

The 2013 National Survey on Drug Use and Health (NSDUH) reports sources of non-medical use of painkillers (Figure 2). More than half (53%) of respondents said that they procured the medication for free from a relative or friend and nearly 15% said that they either bought it from a friend or took the medication without their consent. The primary source of the drug was a medical provider. [53]

Source Where User Obtained

More than One Doctor (2.6%)   Free from Friend/Relative (53.0%)
One Doctor (21.2%)

Source Where Friend/Relative Obtained
One Doctor (83.8%)

Other[1] (4.3%)
Bought on Internet (0.1%)
Drug Dealer/Stranger (4.3%)

More than One Doctor (3.3%)
Free from Friend/Relative (5.1%)
Bought/Took from Friend/Relative (4.9%)

Bought/Took from Friend/Relative (14.6%)

Drug Dealer/Stranger (1.4%)
Other[1] (1.2%)
Bought on Internet (0.3%)

Figure 2 –Source Where Pain Relievers Were Obtained for Most Recent Nonmedical Use among Past Year Users Aged 12 or Older: 2012-2013[53]

Literature suggests that prescription opioid use by a family member could result in unintentional overdose episodes in their dependents. In children, 12% of all drug exposures are attributable to

prescription opioid analgesics. [54] Opioid overdose events in children are often a result of children finding and ingesting medications that were intended for adults. [55]

Opioid analgesics are one of the classes of drugs most commonly abused by Americans 14 years and older. [56] Of those who abuse prescription analgesics, 55% reported getting it from a relative or a friend and approximately 5% reported taking them from a friend or relative without their consent. [57] Increased prescribing of opioids in patients with pain leads to the greater access to these drugs for their dependents. This increases the chances of overdoses in users as well as their dependents.

Resource utilization

The National Poison Data System (NPDS) records "exposures", which are calls to a poison center when an individual has been exposed to an opioid. A report released by NPDS in 2010 indicates that nearly one in every four opioid exposures results in an admission to a health care facility. [58] According to a Center for Disease Control and Prevention (CDC) report, for each unintentional poisoning death due to an opioid analgesic, nine people are admitted for substance abuse treatment, 35 people visit the emergency department, 161 people report drug abuse or dependence and 461 report non-medical uses of opioids. [34]

Long-term effects of opioid overdose

Episodes that do not result in death may contribute significantly to the morbidity of the patients. While administering naloxone may reverse most symptoms related to the overdose, little is known about the long-term impact of overdoses on an individual's organ systems. Non-fatal

episodes can lead to cerebral hypoxia, pulmonary edema, pneumonia and cardiac arrhythmia that may result in prolonged hospitalizations. Overdoses may also lead to muscular impairment and neurological damage and the number of overdoses experienced is a significant predictor of poorer cognitive performance. Surviving an overdose greatly increases the risk of dying from a later overdose. Overall, morbidity is likely to be greater among older, more experienced and dependent users [59,60]

Summary

In conclusion, the increased rate of opioid prescribing has led to an opioid epidemic in the United States. Increased prescribing has led to an increase in opioid diversion as well. The number of fatal and non-fatal overdoses have increased significantly, not only in prescription opioid users but in abusers as well. The overall trend of increasing deaths from prescription opioid use and decreasing deaths from illicit drug use in the past several years has been noted across most literature – this is indicative of the magnitude of the opioid epidemic.[24,61–63]

The high prevalence of opioid overdoses has led to increased resource utilization and healthcare costs. While other studies have examined costs associated with opioid overdoses, no study has examined the cost associated with the downstream costs of opioid overdoses.[4,64–66] This will be discussed in greater detail in Chapter 2.

The goal of this study was to estimate the prevalence, the costs associated with opioid overdose events and the downstream costs associated with an opioid overdose in three distinct populations based on the source of opioid – patients who had their own opioid prescription (prescription opioid users), patients who had a family member with an opioid prescription and patients who did not have an identifiable source of their prescription (non-users).

CHAPTER II:

Literature Review

Literature review summarizing the prevalence of opioid overdoses, source of drugs in opioid overdoses and cost associated with opioid overdoses

A literature review for this study was completed in June 2016.

The objective of this study was to estimate the prevalence and incremental cost and resource utilization for two groups of patients – prescription opioid users who suffer from a prescription opioid overdose and non-users who suffer from a prescription opioid overdose (family members and others).

Since the first aim of this study dealt with prevalence, we conducted a literature review to summarize the prevalence of opioid overdoses in the United States.

Further, we made an assumption that patients who do not have their own prescription but suffer from an overdose use diversion as a means to obtain the prescription opioid. To better understand this area, we conducted a literature review to identify the sources of medications in patients who suffer from an opioid overdose.

Finally, to assess gaps in literature and subsequently compare our findings to other estimates, we conducted a literature review to summarize the studies that have estimated costs associated with opioid overdoses in the United States.

Two databases were used for the literature review – MEDLINE and CINAHL. First, MEDLINE was searched via PubMed for relevant studies from a combination search of search strings that comprised MeSH terms and keywords. CINAHL database via EBSCO host was searched using a combination search of similar keywords to identify additional articles.

After we obtained articles using the appropriate search terms (described below for each section respectively), titles and abstracts were first screened for inclusion criteria and exclusion criteria for each section respectively. After applying the exclusion criteria, article reference lists from included studies and review articles were evaluated for eligibility for inclusion in the literature review.

Section 2.1 – Prevalence of opioid overdoses

The search terms used to identify literature for this literature review are presented in Table 2.

Table 2 – Search terms used to identify literature for the prevalence of opioid overdoses

Search terms	Articles
((Analgesics, Opioid/overdose* OR Analgesics, Opioid/poisoning*) AND (Prevalence))	902
((Analgesics, Opioid/overdose* OR Analgesics, Opioid/poisoning*) AND (Hospitalization))	90
((Analgesics, Opioid/overdose* OR Analgesics, Opioid/poisoning*) AND (Emergency Service, Hospital/utilization*))	9
	1003

The inclusion and exclusion criteria applied were as follows –

Inclusion criteria:

Studies evaluating the prevalence of opioid overdoses.

Exclusion criteria:

1. Evaluated prevalence of overdoses for other illicit drugs and opioids

2. Included codes for adverse effect of opioids along with overdose codes or evaluated prevalence of ER visits and inpatient visits in general

3. Only evaluated overdose death rates

4. Only evaluated trends or changes in opioid overdose patterns and did not report the prevalence

5. Studies not conducted in the United States

This search yielded a total of 1003 articles of which 6 studies fit the eligibility criteria. These studies are summarized in Table 3. In addition, a review article was also assessed for other relevant articles that might have been missed in the search.[67]

Table 3 – Summary of findings for prevalence of opioid overdoses

Author	Database	Patient Group (if any)	Setting	Results
Fulton-Kehoe et al.[68]	WA Medicaid 2006-2010	Medicaid	ER visits and/or inpatient visits	2006 – 416 per 100,000 opioid users 2010 – 492 per 100,000 opioid users
Hasegawa et al. [64]	SEDD 2010-2011 SID 2010-2011	18 years and older	ER visits	50.5 per 100,000 population (includes Heroin)
Inocencio et al. [4]	DAWN 2009	-	ER visits	130.5 per 100,000 population
Fulton-Kehoe et al. [69]	WA worker's compensation system 2004-2010	Non-federal workers in WA who were prescribed an opioid	ER visits and/or inpatient visits	WA workers – 2004 – 3.6 per 10,000 opioid users 2010 – 3.4 per 10,000 opioid users
	NIS 2004-2010	National sample	Inpatient visits	National Sample – 2004 – 2.7 per 100,000 persons 2010 – 12.6 per 100,000 persons
White et al.[70]	NIS 1998-2008	18-24 years	Inpatient visits	1999 – 21.4 per 100,000 population 2008 – 47.68 per 100,000 population
Braden at al. [71]	HealthCore Arkansas Medicaid 2000-2005	Chronic opioid therapy 18 years and older	ER visits	HealthCore* – 241.6 per 100,000 chronic opioid users Medicaid* – 354.3 per 100,000 chronic opioid users

WA = Washington State; SEDD = State Emergency Department Database; SID = State Inpatient Database; DAWN = Drug Abuse Warning Network; ER = Emergency Room; NIS = National Inpatient Sample; NHAMCS = National Hospital Ambulatory Medical Care Survey; NAMCS = National Ambulatory Medical Care Survey; NSDUH = National Survey on Drug Use and Health; *These rates were not presented in the paper, but were estimated based on the information in Table 2 of their study.

Summary of Literature

Fulton Kehoe et al. [68]

The objective of this study was to assess the impact of the implementation of the WA State Opioid Guidelines of 2007 on opioid poisoning rates using Medicaid data. They also examined prescription history before the poisoning events.

The study sample consisted of individuals who had at least 1 claim for an opioid prescription in the Medicaid fee-for-service system during the study period (April 2006 and December 2010).

Opioid poisoning events were identified using ICD-9-CM codes for poisonings (965.00, 965.09 and 965.02) from ER and inpatient hospital claims.

Methadone poisonings rates were 10 times higher than those of other prescription opioid poisonings and increased between 2006 and 2010. The prevalence of poisonings leveled off after implementation of the WA opioid guideline in 2007. The rates of opioid poisonings from 2006-2010 were 416, 485, 491, 492 and 492 per 100,000 users respectively.

Hasegawa et al. [64]

The goal of the study by Hasegawa et al. was to quantify the rate of ER visits for opioid overdoses and understand the association between frequent ER visits for overdose and inpatient visits, near-fatal events, and in-hospital mortality.

The databases used for this analysis were the Healthcare Cost and Utilization Project (HCUP) State Emergency Department Databases (SEDD) and State Inpatient Databases (SID) for

California and Florida (2010-2011). The SEDD contains data for all treat-and-release and transfer ER visits from short-term, acute care, nonfederal, community hospitals in participating states. The SID contains information about all inpatient discharges from short-term, acute care, nonfederal, general, and other specialty hospitals in participating states, including those discharges admitted from the ER.

Opioid poisoning events were identified using ICD-9-CM codes for poisoning by opiate drugs and related narcotic drugs (code 965.0x) in the primary or secondary diagnosis fields.

The rate of ER visits for opioid overdose was 50.5 per 100,000 population (including heroin). While nearly half of ER visits for opioid overdose resulted in an inpatient visits, a prevalence rate for inpatient visits was not reported.

Inocencio et al. [4]

Inocencio et al. estimated weighted prevalence estimates for prescription opioid-related poisoning using Drug Abuse Warning Network (DAWN) data from 2009. Poisoning cases were identified from cases classified as suicide attempt, overmedication, malicious poisoning, or a category labeled "other." Cases who were referred to detoxification, admitted to a chemical dependency or detoxification setting, or psychiatric unit were excluded.

The prevalence of all opioid poisoning visits to the ER was estimated to be 534,490 or 174 per 100,000 population. Approximately 75% (130.5 per 100,000) of all opioid poisoning visits involved non-heroin opioids, while the rest involved heroin and combinations.

Fulton-Kehoe et al., 2013[69]

In this study, prevalence was analyzed using two databases – the WA workers' compensation system and the Nationwide Inpatient Sample (NIS) data. The WA workers' compensation database insures approximately two-thirds of non-federal workers in Washington and includes all medical, hospital, and pharmacy bills for State Fund workers' compensation claims.

Poisonings (overdoses) were identified using ICD-9-CM codes for opioid poisonings (965.00, 965.02, 965.09, E850.1 and E850.2) from the WA worker's database. It is not clear as to whether the same codes were used to identify events in the NIS data as well.

The rate of opioid poisonings among prescription opioid users in WA remained relatively steady from 2004 (3.6/10,000) through 2010 (3.4/10,000).

There was a significant increase in the prevalence of opioid poisonings from 1993 (2.7 per 100,000 persons) to 2010 (12.6 per 100,000 persons) nationally. From 2004-2010, the national rate of opioid poisonings increased by 72%.

White et al., 2011[70]

This study estimated the numbers, rates, and costs of inpatient hospital stays due to alcohol overdoses, drug overdoses and their co-occurrence in 18- to 24-year-olds using the NIS data.

The definition of drug overdoses (identified by ICD-9-CM codes) included poisoning by drugs, medicinals, and biological substances; accidental poisoning by drugs, medicinals, and biological substances; suicide and self-inflicted poisoning by drugs and medicinals; homicidal poisoning by drugs and medicinal substances; and/or poisoning by drugs and medicinals, undetermined

whether accidentally or purposely inflicted. They found that the rates of hospitalization as a result of drug overdoses on prescription opioid pain medications (for example, Oxycodone/acetaminophen, hydrocodone/acetaminophen, oxycodone, codeine, meperidine and morphine) increased 122% between 1999 (rate = 21.44 per 100,000 population) and 2008 (rate = 47.68 per 100,000 population)

The authors did not estimate the costs specifically due to prescription opioid overdoses.

Braden et al., 2010[71]

The aim of the study was to estimate the association between chronic opioid therapy and adverse outcomes. This study used administrative claim records from Arkansas Medicaid and HealthCore commercially insured enrollees, 18 years and older, who used prescription opioids for at least 90 continuous days within a 6-month period between 2000 and 2005 and had no cancer diagnoses.

While the prevalence of overdoses was not reported, it was calculated using data from Table 2 (Twelve-Month Health Service Utilization by Adult Enrollees Who Used Opioids Continuously for 90 Days or Longer During a 6-Month Period From 2000 to 2005) in the study.

The prevalence of ER visits due to opioid overdose among chronic opioid users in the HealthCore database was estimated to be 241.6 per 100,000 while that in the Medicaid database was 354.3 per 100,000 over the five-year period from 2000 to 2005.

Conclusions

Fulton Kehoe et al., 2015 and Braden et al., 2010 estimated the prevalence of overdoses in the Medicaid population. Fulton Kehoe et al. reported prevalence for ER visits and/or inpatient visits while Braden et al. reported prevalence for ER visits. Fulton Kehoe et al. estimated the prevalence in all WA Medicaid patients to be 492 per 100,000 opioid users in 2010. [68] Braden et al. found the prevalence of ER visits to be 354.3 per 100,000 in chronic opioid therapy patients over a 5 year period (200-2005) in the Arkansas Medicaid population. Additionally, in the only study so far to report the prevalence of ER visits due to opioid overdoses in commercially insured enrollees, Braden et al. reported the prevalence to be 241.6 per 100,000 in patients on chronic opioid therapy. [71]

Two studies used the NIS to estimate the prevalence of hospitalizations due to opioid overdose. Fulton Kehoe et al., 2013 estimated the national prevalence of hospitalizations due to opioid overdoses to be 12.6 per 100,000 persons in 2010 while White et al. estimated the prevalence of hospitalizations due to opioid overdose to be 47.68 per 100,000 population in 18-24 year olds. Part of the discrepancy is due to use of different ICD codes used to identify overdoses in each of the studies. Neither of the studies clearly specified which ICD codes were used to identify overdose events. Additionally, prevalence for different age groups was estimated in each of the studies respectively [69,70] Fulton-Kehoe et al. also estimated the prevalence of ER visits and/or inpatient visits for opioid overdoses and report a prevalence of 3.4 per 10,000 opioid users in 2010. The codes used for this analysis were clearly stated. [69]

Hasegawa et al., 2014 estimated the prevalence of ER visits for all opioid overdoses in California and Florida and report it to be 50.5 per 100,000 population. This rate also includes overdoses due to heroin.[64]

Finally, Inocencio et al., 2013 report the prevalence of prescription opioid overdoses in a national sample to be 130.5 per 100,000 population using DAWN 2009 data. These results might not match other studies that use administrative data to estimate overdoses because DAWN has a different system of identifying and classifying overdoses. Cases in DAWN were categorized into 8 types of cases – these include suicide attempt, seeking detoxification, alcohol only, adverse reaction, overmedication, malicious poisoning, accidental ingestion and other. Inocencio et al. defined opioid-related poisoning cases that were classified in DAWN as suicide attempt, overmedication, malicious poisoning or a category labelled "other". [4]

Due to differences in the methodology used to identify opioid overdoses using claims data and different populations studied, we cannot make direct comparisons between prevalence estimates obtained from these studies.

Section 2.2 - Source of prescription opioid in prescription opioid overdoses

The search terms used for this literature review are presented in Table 4.

Table 4 - Search terms used to identify literature for the source of prescription opioid in opioid overdoses

Search terms	Articles
((Analgesics, Opioid/overdose* OR Analgesics, Opioid/poisoning*) AND (source of drug OR source of medication))	55
((Analgesics, Opioid/overdose* OR Analgesics, Opioid/ poisoning*) AND (source of prescription drug OR source of prescription medication))	21
((Analgesics, Opioid/overdose* OR Analgesics, Opioid/ poisoning*) AND (access to medication OR access to drug))	72
((Analgesics, Opioid/overdose* OR Analgesics, Opioid/ poisoning*) AND (obtain medication OR obtain drug))	22
((Analgesics, Opioid/overdose* OR Analgesics, Opioid/ poisoning*) AND (Prescription Drug Misuse*/statistics & numerical data))	36
	206

The inclusion and exclusion criteria applied were as follows –

Inclusion criteria:

1. Studies that reported the source of prescription opioid in case of an opioid overdose

2. Studies that reported source of opioid for abuse or non-medical use

Exclusion criteria:

2. Studies not conducted in the United States

This search yielded a total of 206 articles of which twelve studies fit the eligibility criteria.

These studies are summarized in Table 5.

Table 5 – Summary of findings for source of opioid in prescription opioid overdoses

Author	Data Source	Results*
Baumblatt et al.[72]	Tennessee Controlled Substances Monitoring Program (TNCSMP) data 2007-2011	Increased risk of opioid-related overdose death was associated with 4 or more prescribers, 4 or more pharmacies, and more than 100 MMEs (Morphine Milligram Equivalents). People with 1 or more risk factor accounted for 55% of all overdose deaths.
Frank et al.[73]	Interviews with young adults (18-32 years) who reported nonmedical prescription opioid use in the past month (New York City)	Study participants stated that their initial prescription opioid use was due to the widespread availability in a household setting and the perception of being relatively harmless and less addictive as compared to heroin since they were given the status of a "medication".
National Survey on Drug Use and Health[53]	Survey of a representative sample of U.S. civilian, noninstitutionalized population (12 years or older)	More than half of non-medical users (53%) obtained the opioid prescription free from a friend or family, 21% obtained the prescription from a doctor and nearly 15% bought it or took it from a friend or relative.
Johnson et al.[74]	Interviews with family or close friends of the deceased 2008-2009	The source of prescription opioids for people who suffered from opioid-related deaths was a healthcare provider in majority of cases (91.8 %). Other sources (not mutually exclusive) included: for free from a friend or relative (24%), from someone without their knowledge (18.2%), purchase from a friend, relative, or acquaintance (16.4 %) and purchase from a dealer (not a pharmacy) (11.6 %)
Lanier et al.[75]	Interviews with family or close friends of the deceased 2008-2009	Obtaining prescription pain medication from a non-prescription source was 4.3 times more common among decedents as compared to respondents who reported prescription opioid use during the previous year (35.8% vs. 8.3%).
CDC. Morbidity and Mortality Weekly Report. [76]	Utah Controlled Substance Database (CSD) Utah Poison Control Center (PCC) 2002-2011	There were 462 exposures attributable to buprenorphine, of which 3 led to death.
Ogle et al.[77]	Medical Examiner files (Florida) Toxicology reports	A total of 155 accidental deaths listed oxycodone as a cause of death, of which more than half (52.9%) did not have prescriptions

	2009	for oxycodone.
Lankenau et al.[78]	Interviews with young IDUs (16-25 years) (Los Angeles and New York)	Initiation into opioid misuse was facilitated by easy access to one's own prescription (16%), family member's prescription (22%) and friends' and acquaintances' prescription (62%).
Weimer et al.[79]	Office of The Chief Medical Examiner files Virginia Prescription Monitoring Program 2004	A total of 61 methadone-related overdose deaths were identified. The majority of methadone overdose deaths in this study were related to illicit methadone use (67%); 28% of the decedents were prescribed opioids.
Cicero et al.[80]	Survey of prescription opioid dependent patients entering drug treatment programs	The study population was divided into groups – Health Care professionals (HC) and Non-Health Care professionals (NHC). The HC group was more likely to use doctors' prescriptions and forged prescriptions. The NHC group was more likely to use dealers or a friend or relative to obtain the prescription opioid.
Bailey et al.[81]	Poison centers participating in the RADARS System 2003-2006	A total of 9,179 exposures in children under 6 years were identified; 92% occurred in the home. Exposures were associated with 8 deaths, 43 major effects, and 214 moderate effects.
Green et al.[82]	Abusers identified from the ASI-MV® Connect database	Women abusers were more likely to obtain their prescription opioids from family, friends, acquaintances or their own prescriptions whereas men abusers were more likely to obtain them from dealers.
Shah et al.[83]	Medical Examiner files (New Mexico) 1998-2002	Of 143 methadone-related deaths, 22.4% were attributable to methadone alone, 23.8% were due to methadone/prescription drugs (no illicit drugs), 50.3% were due to methadone/illicit drugs and 3.5% were due to methadone/alcohol. Of 79 decedents (55.2%) with a known source of methadone, 86% obtained methadone through a physician prescription.

CDC = Center for Disease Control and Prevention; RADARS = Researched Abuse, Diversion and Addiction-Related Surveillance; IDU = Injection Drug User; ASI-MV Connect = Addiction Severity Index Multimedia Version Connect
*Results pertinent to source of opioid in opioid overdoses are reported

Summary of Literature

Baumblatt et al.[72]

The objective of this matched case-control study was to identify risk factors associated with opioid-related overdose deaths. [72] The Tennessee Controlled Substances Monitoring Program collects patient information for all prescriptions of controlled substances (Schedules II to IV). Cases were identified as patients who had suffered from an opioid-related death during the study period (January 1, 2009 – December 31, 2010) who had one or more opioid prescription in the 12 months before their death. For each case patient, 20 live controls were selected by random-number generation. Controls were patients with 1 or more opioid prescriptions during the 12 months before the date of death of the matched case patient. The authors found that of all people in Tennessee prescribed opioids during 2011, 7.6% used more than 4 prescribers, 2.5% used more than 4 pharmacies, and 2.8% had a mean daily dosage greater than 100 morphine milligram equivalents (MME).

Increased risk of opioid-related overdose death was associated with 4 or more prescribers, 4 or more pharmacies, and more than 100 MME. People with 1 or more risk factor accounted for 55% of all overdose deaths.

Frank et al. [73]

This was a qualitative study in which 46 young adults (ages 18-32) from New York City who had engaged in non-medical prescription opioid use in the past 30 days were interviewed. The interviews were in-depth, semi-structured and audio recorded. While the goal of the study was to

understand the overdose knowledge and experience of non-medical prescription opioid users, the results briefly discussed opioid initiation and source of opioid at the time of initiation.

The authors reported that the study participants' early impressions of prescription opioids were that they were relatively harmless and as compared to heroin, less likely to result in an overdose. Since these opioids were accessible in a household setting and they had "medication" status, the participants viewed these as less addictive and began using them.

Results from the 2013 National Survey on Drug Use and Health (NSDUH): Summary of National Findings[53]

NSDUH is the primary source of statistical information on the use of illegal drugs, alcohol, and tobacco in the United States civilian, noninstitutionalized population aged 12 or older. This survey has been conducted by the Federal Government since 1971. The surveys were conducted through face-to-face interviews with a representative sample of the United States population. The data was collected from residents of households, non-institutional group quarters (for example – shelters, dormitories and rooming houses) and from civilians living on military bases.

Among the study participants who used prescription opioids non-medically in the past year, 53% reported that they obtained the medication for free from a friend or relative, 21% obtained the medication from one doctor and 15% bought or took it from a friend or relative without their knowledge (Figure 2). For the 53% who obtained the opioid from a friend or relative, 84% were prescribed the opioid by one doctor.

Johnson et al.[74]

The objective of the study by Johnson et al. was to identify characteristics related to unintentional prescription opioid overdose deaths in Utah.

Decedents were identified from records of the Utah Office of the Medical Examiner (OME) in Utah from October 2008 to October 2009. Manner and causes of death were determined by OME on the basis of scene-of-death investigation, autopsy, and toxicology findings. Decedents were included in the study if they were Utah residents aged 18 years or older, had a manner of death characterized by the OME as either unintentional or undetermined, had a prescription opioid listed as a cause of death and did not have a violent event (e.g., fall or drowning) as a cause of death.

Interviews were conducted by trained interviewers by telephone, with persons who were identified by OME death-scene investigators as either next of kin or best person to contact. The questions were based on the deceased's chronic conditions, chronic pain, prescription medication use, healthcare providers and mental health amongst others.

The source of prescription opioids was from a healthcare provider in most of the cases (91.8 %). Other sources (not mutually exclusive) included: for free from a friend or relative (24%), from someone without their knowledge (18.2%), purchase from a friend, relative, or acquaintance (16.4 %) and purchase from a dealer (not a pharmacy) (11.6 %).

<u>Lanier et al.</u>[75]

The goal of this study by Lanier et al. was to identify the risk factors for prescription opioid deaths in Utah. The study design is similar to the study carried out by Johnson et al.[74], with the inclusion of a control group.

Controls were identified from the Utah 2008 Behavioral Risk Factor Surveillance System (BRFSS), a survey database maintained by the Utah Department of Health (UDOH) in partnership with the Center of Disease Control and Prevention (CDC). Respondents who reported prescription opioid use during the previous year were selected as controls for this study. BRFSS 2008 contained information regarding the use of prescription pain medications during the past year, their pattern of use (as prescribed or other) when last prescribed, their source (by prescription from a health care provider, a nonprescription source, or both), names of medications, and the presence of chronic pain.

Approximately 90% of both groups had obtained their prescription pain medication by prescription from a health care provider. Of those decedents who obtained their prescription medication through a prescription, 52.9% used their medications more often or in higher quantities than prescribed whereas only 3.2% of their comparison group misused their medication.

Obtaining prescription pain medication from a non-prescription source was 4.3 times more common among decedents as compared to the control group (35.8% vs. 8.3%).

Center for Disease Control and Prevention, Morbidity and Mortality Weekly Report, 2012 [76]

This report by the CDC estimates the prevalence of exposures attributable to buprenorphine in Utah from 2002 to 2011. The Utah Controlled Substance Database (CSD) and the Utah Poison Control (PCC) data were used for this study. The CSD tracks all outpatient prescriptions for Schedule II–V drugs dispensed in Utah. The PCC maintains data on reported human exposures to buprenorphine and other drugs (including intentional and unintentional, therapeutic and nontherapeutic exposures). Standardized information collected for each exposure includes age, sex, substance, route of exposure, reason for exposure, location of exposure, location of caller, therapy provided, clinical effects, management location, and medical outcome. Exposures can be any kind of exposure to an opioid, from holding the medication to ingestion.

A total of 462 exposures to buprenorphine were recorded in the PCC database from 2002-2011. Of all the exposures, 54% were in adults 20 years and older, 39% were in children less than 5 years and 7% were among the 6-19 year age group.

Of all the exposures, 3 (less than 1%) resulted in respiratory arrest in children.

Ogle et al., 2012[77]

Ogle et al. analyzed toxicological findings of accidental deaths involving oxycodone in an effort to identify the source of medication that resulted in these deaths.

Medical Examiner files and toxicology reports from 2009 were used to assess demographic and clinical characteristics of the decedents as well as the presence and concentration of oxycodone and other drugs.

All oxycodone-related deaths were included in this study. These were cases when (1) oxycodone was the primary or contributory cause of death (n = 117), as well as those where (2) oxycodone was the incidental cause of death (n = 38).

A total of 155 deaths were identified. More than half of the population (52.9%) did not have prescriptions for oxycodone.

Lankenau et al., 2012

The goal of this exploratory qualitative study was to describe patterns of initiation into prescription opioid misuse. The study participants were 50 young injection drug users (IDUs) aged 16-25 years from Los Angeles and New York who had misused a prescription opioid at least three times in the past three months.

They found that Vicodin (hydrocodone and acetaminophen) was the drug most commonly used at initiation, followed by OxyContin (oxycodone) and Percocet (oxycodone and acetaminophen). Three sources of the prescription opioid at the time of initiation were reported – misusing a family member's prescription, misusing one's own prescription and misusing a prescription obtained from a friend or an acquaintance.

While 60% of study participants grew up in households or visited extended families where opioids were prescribed, one-third reported initiating opioid use with an opioid taken from a family member. Also, nine participants reported that they misused a family member's prescription after initiating misuse via other sources.

Nearly 75% of study participants were prescribed opioids for pain conditions such as dental procedures and sports injuries of which 22% reported using their own prescription as the source of the first opioid misuse.

A majority of the participants (62%) reported acquiring the drug of initiation from a friend or acquaintance. The friends or acquaintances often obtained the drugs from their family members or used their own.

Weimer et al., 2011 [79]

Weimer et al. describe case series of patients who died from methadone poisoning or overdose in rural western Virginia during 2004. They also compare cases according to the source of methadone.

Three data sources were used for this study – medical examiner records, Opiate Treatment Programs (OTP) medical records, and Virginia Prescription Monitoring Program (PMP) database records.

For this analysis, all cases occurring during the study period, where the cause of death was poisoning, were identified for possible inclusion in the study. Methadone-related cases were defined as those deaths where the manner of death was intentional and unintentional, methadone was present in the toxicological analyses, and methadone was found to be a direct or contributing cause of death by the medical examiner. For each decedent, the possible sources of methadone were prescribed by a non-OTP physician, prescribed by an OTP-physician, or illicit.

A total of 61 methadone-related overdose deaths were identified. The majority of methadone overdose deaths in this study were related to illicit methadone use (67%); 28% of the decedents were prescribed opioids and 5% of the decedents obtained it from an OTP.

Cicero et al., 2010 [80]

Cicero et al. examined whether the frequency of misuse of fentanyl and other opioids in the real world matched their predicted potential abuse from abuse liability assessments. A total of 1,818 prescription opioid dependent patients entering drug treatment programs were recruited in this study. Participants were included in the study if they had a diagnosis for prescription opioid analgesic abuse or dependence using the DSM – IV criteria and if they used prescription opioids once in the past 30 days to get high. The participants were asked to complete an anonymous survey that covered their drug use and health-related issues.

The study participants were divided into two groups – 196 Health Care professionals (HC) and 1,622 Non Health Care professionals (NHC). The authors reported that the HC group was more likely to use doctors' prescriptions and forged prescriptions when they abused prescription opioids. In comparison the NHC group was more likely to use a dealer or prescriptions obtained from friends or families. Other sources that were not significantly different between the two groups were stolen prescriptions, prescriptions obtained from the ER and opioids bought on the internet.

Bailey et al., 2009 [81]

The goal of this study was to estimate the impact of opioid abuse on overdoses in children.

Data from poison centers participating in the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System was analyzed for children under 6 years for 7 opioids from January 2003-June 2006.

Exposures represent a range of behaviors, from holding the medication to ingestion. Exposures and associated medical outcomes were characterized with an opioid 'mention' as the unit of analysis. Each mention represents a prescription opioid to which a child was exposed and for which information was gathered through a call to a participating poison center. Moderate effects were those where the symptoms were not life threatening; major effects were instances where the patient exhibited symptoms that were life threatening or resulted in disability or disfigurement.

A total of 9,179 exposures were identified; 99% of the exposures involved ingestion and 92% occurred in the home. Exposures were associated with 8 deaths, 43 major effects, and 214 moderate effects.

Green et al., 2009 [82]

The goal of this study was to describe characteristics of women who abuse prescription opioids and to contrast gender differences among prescription opioid abusers. Addiction Severity Index Multimedia Version® (ASI-MV®) Connect is a continuous real-time data stream that collects data on substances used and abused by adult clients (18 years or older) entering substance abuse treatment across various centers in the United States. Data for patients that completed the ASI-

MV® was used to identify the study sample. The study sample consisted of 3,821 assessments of people entering substance abuse treatment from November 2005 to March 2008 who reported abuse of prescription opioids in the past month.

Women reported that their prescription opioids were more likely obtained from family, friends or acquaintances or from their own prescriptions, whereas men reported obtaining prescription opioids from dealers.

A high percentage of both men and women reported obtaining prescription opioids from a dealer. Other sources of prescription opioids that were mentioned were multiple doctors, stealing and internet. The other sources represented less than 15% of responses.

Shah et al., 2005 [83]

One of the objectives of the study was to characterize methadone-related deaths.

Overdose deaths from the Medical Examiner file in New Mexico were examined from 1998-2002. All unintentional drug overdose decedents who were residents of and died in New Mexico from 1998 to 2002 and for whom methadone was cited as a cause of death, alone or in combination with another drug (illicit and/or prescription), were classified as methadone-related deaths. The circumstances of death and the decedent's medical and drug use history (if present) were collected by abstractors using a standard data collection form. Data for circumstances of death included location of overdose, day of the week death was pronounced, evidence of injection drug use (IDU) at the scene (defined by presence of track marks or syringe at the scene), source of methadone and reason for ingestion (pill bottle with decedent's name, medical records), and methadone blood concentration. Data for history of drug use were collected when

available from medical records and family history. History of drug use included illicit drug use, non-medicinal use of prescription drugs, IDU and previous overdose.

Of 143 methadone-related deaths, 22.4% were attributable to methadone alone, 23.8% were due to methadone/prescription drugs (no illicit drugs), 50.3% were due to methadone/illicit drugs and 3.5% were due to methadone/alcohol.

The source of methadone was available for 79 decedents; 68 decedents (86%) had a physician prescription for methadone and 11 decedents (7.7%) obtained diverted methadone (either purchased 'off the street' or obtained from a prescription for someone else). The source of methadone for 44.8% of the sample was not indicated.

Conclusions

The above studies suggest that this is an extremely complex area. Patients who misuse or abuse opioids and/or suffer from an overdose obtain their medications from a wide variety of sources – from friends and relatives to multiple pharmacies and prescribers to illicit drugs. The geographical variation in the studies also suggests that this problem affects many regions of the United States.

A majority of the studies that identified a source of the overdose, identified them for deceased patients. The other two studies identified exposures in children. Ours is the first study that identifies a potential source of opioid for overdoses based on family-level data.

Section 2.3 – Costs associated with prescription opioid overdoses

The search terms used for this literature review are presented in Table 6.

Table 6 - Search terms used to identify literature for the costs associated with prescription opioid overdoses

Search terms	Articles
((Analgesics, Opioid/overdose* OR Analgesics, Opioid/poisoning*) AND (Cost))	68
((Analgesics, Opioid/overdose* OR Analgesics, Opioid/ poisoning *) AND (Healthcare costs))	17
((Analgesics, Opioid/overdose* OR Analgesics, Opioid/ poisoning *) AND (Costs and Cost Analysis))	21
	106

The inclusion and exclusion criteria applied were as follows –

Inclusion criteria:

Evaluated costs attributed to opioid overdose

 Exclusion criteria:

1. Evaluated costs due to opioid abuse, misuse or dependence

2. Evaluated cost-effectiveness of opioid analgesics

3. Studies not conducted in the United States

This search yielded a total of 106 articles of which the 1 study fit the eligibility criteria

(Inocencio et al., 2015.) The other three studies were obtained during the search in section 1

because they were not pulled up by the section 3 search terms. These studies are summarized in

Table 7.

Table 7 – Summary of findings for costs associated with prescription opioid overdoses

Author	Opioid Use	Data Sources	Costs	Results
Hasegawa et al.[64] (2014)	"Opioid overdoses"	SEDD 2010-2011 SID 2010-2011	ER and Inpatient charges	Median ER charges per patient – $4,521 Median inpatient charges per patient – $22,460 $208 million for total ER and inpatient charges annually
Yokell et al.[65] (2014)	"Prescription Opioid Overdoses"	NEDS 2010	ER and Inpatient charges	Average ER charges – (prescription opioids*) $3,640 Average inpatient charges – (prescription opioids*) $29,497
Inocencio et al.[4] (2013)	"Opioid-related poisoning"	DAWN 2009 NEDS 2009 NIS 2009 GAO Report 2006 Red Book 2012 NVSS 2009	Direct and indirect costs	Direct costs – Average cost per poisoning event (prescription opioids*) – $4,255 Indirect costs – Average costs per poisoning event (prescription opioids*) – $34,825 $20.4 billion total costs annually

SEDD = State Emergency Department Database; SID = State Inpatient Database; DAWN = Drug Abuse and Warning Network; NEDS = Nationwide Emergency Department Sample; ER = Emergency Room; NIS = National Inpatient Sample; GAO = Government Accountability Office Report; NVSS = National Vital Statistics System; *Since these studies report costs incurred due to heroin overdoses as well, the costs listed in the above table are specifically incurred due to an overdose from a prescription opioid.

Summary of literature

<u>Hasegawa et al., 2014</u> [64]

The goal of the study by Hasegawa et al. was to quantify the rate of ER visits for opioid overdoses (including heroin) and understand the association between frequent ER visits for overdose and hospitalizations, near-fatal events, and in-hospital mortality.

This was a retrospective population-based cohort study that utilizes encounter data abstracted from the Healthcare Cost and Utilization Project (HCUP) State Emergency Department Databases (SEDD) and State Inpatient Databases (SID) for the states of California and Florida for 2010 and 2011. These databases capture all ER visits regardless of disposition and with information on short-term outcomes for patients admitted through the ER. The study sample included all patients who suffered from an overdose during the study period. Patients who did not have an ER visit in 2010 were excluded since they would not have a 365 day follow-up period. Also, patients who had a gap of more than a year for another ER visit from the index date (first ER visit) were excluded since they wanted to examine the association of frequency of ER visits with other factors.

The cost analysis was carried out for the state of Florida. The total charges for ER and inpatient services for opioid overdoses were estimated to be $208 million annually. When broken down by visits with hospitalization and without, median charges per patient were $4521 in patients without hospitalization and $22,460 in patients with hospitalization. Patients who had 1 or more hospitalizations during the study period were responsible for 93.2% of total charges.

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<u>Yokell et al., 2014</u> [65]

Yokell et al. also used the NEDS sample to describe prescription and non-prescription opioid overdoses, but used 2010 data to obtain weighted prevalence estimates and charges related to overdose events.[65] ER characteristics, demographic and clinical characteristics of the patients and outcomes for prescription and non-prescription opioid overdose events were reported.

ICD-9-CM diagnostic codes and injury codes for prescription opioid (965.02, 965.09, E850.1, E850.2), heroin overdoses (965.01, E850.0) and unspecified opioid (965.00 with no E-code for heroin or prescription opioid overdose) were used to identify opioid overdose events.

ER visits due to prescription opioids constituted 67.8% of all overdoses; 16.1% were due to heroin, 13.4% were a result of unspecified opioids and 2.7% were due to multiple opioid types. Of all patients admitted to the ER for an overdose, 45.3% were treated and released from the ER and 50.6% were admitted to the hospital.

The average charges for an ER visit for an opioid overdose due to prescription opioids was $3,640, for heroin was $3,692 and for unspecified or multiple types of opioid was $4,121.

The total ER and inpatient charges for patients in this sample were estimated to be $2.3 billion annually.

<u>Inocencio et al., 2013</u> [4]

Inocencio et al. evaluated the economic burden of opioid poisonings using a societal perspective.[4] The method of economic evaluation used was the bottom-up approach in which mean estimates of each cost component are multiplied by national estimates of prevalence.

Weighted prevalence estimates for prescription opioid poisonings were obtained from 2009 Drug Abuse Warning Network (DAWN). Direct costs included emergency room (ER) costs, inpatient costs, ambulance costs, drug costs and device costs. ER and inpatient costs were obtained from the Healthcare Cost and Utilization Project (HCUP) 2009 Nationwide Emergency Department Sample (NEDS) and the 2009 National Inpatient Sample (NIS). Ambulance costs were obtained from a 2006 Government Accountability Office (GAO) report.[84] Drug costs were obtained from the 2012 Red Book and costs for syringes and intranasal devices were based on market prices obtained from a medical services supply company.[85,86] A Monte Carlo simulation was used to impute missing costs.

Prevalence of opioid poisoning visits to the ER were estimated to be 174 per 100,000 people; approximately 75% involved non-heroin opioids and 25% involved heroin and combinations. The average direct cost per poisoning event for prescription opioids was estimated to be $4,255 and the indirect costs per poisoning event for prescription opioids were $34,825. The cost per case for prescription opioids was greater than that heroin ($38,541 vs $33,793). Total costs were estimated to be $20.4 billion for that year, with indirect costs constituting 89% of the total costs.

Conclusions

Studies by Hasegawa et al. report median ER and inpatient charges associated with an overdose to be $4,521 and $22,460 respectively.[64] Yokell et al. estimated the mean ER and inpatient charges associated with an overdose to be $3,640 and $29,497 respectively.[65] However, the estimates by Hasegawa et al. also include heroin overdoses. Also, since mean and median values are reported these estimates are not directly comparable, though they are in the same range. Inocencio et al. report the average cost associated with a prescription opioid overdose to be $4,225.[4]

The studies presented above have limitations. An opioid overdose was treated as an acute event and downstream costs subsequent to an opioid overdose were not evaluated. Additionally, while the studies focused on ER and inpatient charges, there are instances when overdose events are resolved outside the hospital setting – these costs were not captured.

As with all the studies using NEDS data, charges for opioid overdoses are reported. These do not reflect the true cost of opioid overdoses and are typically overestimates.

Rationale

To our knowledge, ours is the first study that will estimate and compare the prevalence of opioid overdoses for acute and chronic opioid use. Additionally, we also identified patients who had an opioid overdose and classified them by source of opioid. A majority of the studies that identified a source of overdose, identified them for deceased patients. Ours is the first study that identifies a potential source of opioid for overdoses based on family-level data.

While most studies have identified prevalence based on data for ER visits and/or inpatient visits, we have built on this literature and captured the prevalence of opioid overdoses that were resolved at other places of service – for example, in ambulances or the outpatient setting.

We have captured the downstream costs over a year for patients who suffer from an opioid poisoning event. Since we had all medical claims data, we are also able to capture costs apart from ER and inpatient costs – for example, outpatient costs, laboratory costs and ambulance services, among other healthcare facility costs. Additionally, we have reimbursement costs and not charges, so our estimates will be more accurate.

Prescription data allowed us to identify a control group, i.e., patients with an opioid prescription who did not suffer from a poisoning event. This allowed us to compare the healthcare expenditures between the two groups after adjusting for comorbidities and other risk factors.

We also estimated the cost of opioid poisonings in family members of patients with an opioid prescription as well as the cost of opioid poisoning in patients who do not have an opioid prescription as compared to patients who did not suffer from an overdose. These estimates will add to the literature on opioid diversion.

CHAPTER III

Methods and results for specific aim 1:

Prevalence of opioid overdoses in prescription opioid users, family members of prescription opioid user and others

Section 3.1 – Methods

This section describes the study methodology used to estimate the prevalence of prescription opioid overdoses in prescription opioid users, family members of prescription opioid users and individuals who did not have an opioid prescription themselves and neither did any family member (categorized as "others") between July 2010 and June 2015.

Database

Data for the study consisted of medical and pharmacy claims from SelectHealth. SelectHealth is a not-for-profit health insurance organization serving members in Utah and southern Idaho. SelectHealth is committed to helping people live the healthiest lives possible. SelectHealth offers medical, dental, vision, pharmacy benefit management, and life and disability coverage to its members. We were provided with claims for a subset of patients for this study. The data included medical and pharmacy claims for patients who had at least one opioid analgesic prescription and their families and patients who had an opioid overdose event between July 2010 and June 2015.

In 2015, SelectHealth insured approximately 650,000 patients of the commercial population, 80,000 patients through managed Medicaid and 30,000 through their Medicare Advantage plan. The medical claims file contained all medical claims for a patient, including a claim ID, the date the claim was filed, the diagnosis code and description (in International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) format), the place the service was provided and the allowed cost for each claim. Examples of places of service in the dataset include Emergency Room - hospital (ER), inpatient hospital, outpatient hospital, ambulance – land, hospice and nursing facility. Allowed cost is the reimbursement that the payer paid the provider for the service.[87]

Database elements in the pharmacy claims file included a claim ID, date the claim was filed, medication name, National Drug Code (NDC), Generic Product Identifier (GPI), days' supply, quantity supplied and allowed cost for each claim.

The member data file contained a unique encrypted member ID for each patient that was used to link the patient across the medical and the pharmacy files, their date of birth, sex, and their relationship to the primary cardholder.

Sample selection

The following patients were included in this study –

- All patients who received an opioid in the period from July 2010 to June 2015

- All patients who suffered from at least one opioid overdose event (non-heroin) in the period from July 2010 to June 2015

While cancer patients were not excluded from this analysis, we will report the estimates for number of cancer patients who had an opioid overdose.

Identification of overdose events (ICD codes)

Opioid overdoses were identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (Table 8).

Table 8 – ICD-9 CM codes for overdose events

Code	Description
E850.1	Accidental poisoning by methadone
E850.2	Accidental poisoning by other opiates and related narcotics
965.0	Poisoning by opium (alkaloids), unspecified
965.02	Poisoning by methadone
965.09	Poisoning by other opiates

We used the following conditions to identify a unique opioid overdose event –

If the same patient had two different claims for an overdose on the same day, we considered the two claims to be one event.

When opioid overdose cases had claims that spanned more than 1 day, claim fill dates that were less than 7 days from the first event were considered one event. Subsequent claims that were 7 or more days after the index event were considered a new event. [69]

Identification of prescription opioid users

The pharmacy claims data included a Generic Product Identifier (GPI) and National Drug Code (NDC) for all the drugs. However, since we did not have a key or legend to identify a drug using GPI or NDC, prescription opioids were identified manually. We identified a list of 7,087 unique drugs from which opioids and benzodiazepines were identified manually. Mixed formulations containing an opioid were included in the study as well.

All patients who had a prescription for an opioid during the study period were classified as a prescription opioid user.

Identification of prescription opioid users who suffered from an overdose

To be able to link a prescription to an overdose, we assessed for temporality. In the context of this study, we define an overdose case to be temporal if the patient was prescribed an opioid before the overdose. This could be an active prescription or medication from a prescription within the previous year. A patient who had a prescription for an opioid before they had the overdose were classified as a prescription opioid user who suffered from an overdose.

We chose to use this definition of temporality because there is increasing evidence that leftover opioid pills are not disposed appropriately and are often saved for later and even shared with others. Nearly 62% of people who have leftover opioid pills keep them for later use rather than disposing them. [88]

To create a stronger link between the prescribed opioid and the overdose, we further restricted the definition of temporal overdoses to patients who had an overdose within one year of their most recent prescription opioid fill date.

All patients who had an overdose within 1 year of their most recent prescription opioid fill date were classified as recent prescription opioid users. If patients did not meet this criteria, they were then categorized as family members of prescription opioid users or others as applicable and as explained below.

Identification of Family Members of Prescription Opioid Users who suffered from an overdose

To identify family members of prescription opioid users who suffered from an overdose we created a "family ID" variable based on the encrypted member ID we were given in the data by removing the last digit of the encrypted member ID. For example, patients 101 and 102 belong to the same family with the family ID '10'.

We checked for temporality in this group as well by checking if the family member received their opioid prescription before the patient had an overdose. If yes, then the patient was considered to be a family member of a prescription opioid user who suffered from an overdose from their family member's prescription. If temporality was not established, the patient was considered to be an "other" opioid overdose patients who obtained their prescription opioid from elsewhere. We did not check if the prescription was dispensed within a year before the overdose in this case because we made the assumption that individuals who obtain the medication from

family members can get them at any time and it does not necessarily have to be an active prescription.

Patients who did not have an opioid prescription themselves, but had an overdose and shared the same family ID with a patient who had an opioid prescription fill before the date of the overdose, were classified as family members or dependents of prescription opioid users who suffered from an overdose.

In addition to patients who were categorized as described above, patients who were not categorized as recent prescription opioid users were then assessed to identify if they were family members of patients who had an opioid prescription using the same process described above.

Identification of "Other Overdosers" group – Patients who do not have an identifiable source for their prescription opioid but suffered from an overdose

Patients who did not have a temporal opioid prescription within a year from the date of the overdose, did not have a family member who had an opioid prescription before the date of their overdose but suffered from an overdose were classified as "Other" overdosers. These patients did not have a known and identifiable source for their prescription opioid.

The classification of patients into these three groups is explained in Figure 3.

Morphine Equivalent Daily Dose

For opioids, it is important to convert the strength of all the medications to the standard Morphine Equivalent Daily Dose (MEDD) format so as to be able to compare each medication's potency against a standard – Morphine.

The following method was used to calculate the MEDD –

Step 1 – Quantity/day: For each medication, the quantity was divided by the days' supply to get the quantity per day of the drug consumed.

In case of solid oral dosage forms like tablets or capsules, we rounded down unless the quantity/day was less than 1. If the quantity/day was less than 1, we left the estimate as is.

Step 2 – Amount/day: This was followed by calculating the amount per day, where the strength was multiplied by the quantity/day obtained in step 1.

Step 3 – Morphine equivalents/day: The product of step 2 was then multiplied by the appropriate morphine equivalent conversion factors. A list of these factors are presented in

Table *9.*

We modified this formula to calculate the MEDD for patches. Since the strength is in mcg/hour, we converted the strength to mg/hour and then to mg/day by multiplying it by 24.

Table 9 - Opioid Morphine Equivalent Conversion Factors[89,90]

Major Group	Type of Opioid	Morphine equivalent conversion factor per mg of opioid
Short-acting, less potent (Schedule III/IV)	Propoxyphene (with or without aspirin, acetaminophen or ibuprofen)	0.23
	Codeine + (acetaminophen, ibuprofen or aspirin)	0.15
	Hydrocodone + (acetaminophen, ibuprofen or aspirin) Hydrocodone and homatropine	1.0
	Tramadol with or without aspirin	0.10
	Butalbital and codeine (with or without aspirin, acetaminophen or ibuprofen)	0.15
	Dihydrocodeine (with or without aspirin, acetaminophen or ibuprofen)	0.25
	Pentazocine (with or without aspirin, acetaminophen or ibuprofen)	0.37
Short-acting, more potent (Schedule II)	Morphine sulfate	1.0
	Codeine sulfate	0.15
	Oxycodone (with or without aspirin, acetaminophen or ibuprofen)	1.5
	Hydromorphone	4.0

	Meperidine hydrochloride	0.1
	Fentanyl citrate transmucosal	0.125
	Oxymorphone	3.0
	Tapentadol	0.4
	Opium	1.0
Long-acting (Schedule II)	Morphine sulfate sustained release	1.0
	Fentanyl transdermal	2.4
	Levorphanol tartrate	11.0
	Oxycodone HCL controlled release	1.5
	Methadone	3.0
Schedule III	Buprenorphine patch	12.6
	Buprenorphine tablet or film	10

Benzodiazepine poisoning

Benzodiazepine poisoning was identified using ICD-9CM codes. We identified patients with concurrent use of opioids and benzodiazepine if they had a diagnosis for both opioid overdose and benzodiazepine poisoning on the same day.

Table 10 - ICD-9 CM codes for benzodiazepine poisoning

Code	Description
E853.2	Accidental poisoning by benzodiazepine-based tranquilizers
969.4	Poisoning by benzodiazepine-based tranquilizers

Figure 3 – Categorizing patients into groups based on source of opioid

The flowchart contains the following boxes:

Prescription opioid users who suffered from an overdose (N = 527)

Excluded patients –
1. Not temporal –
i.e. prescription does not precede overdose
(N = 50)

2. The time between the most recent fill and overdose
exceeds 1 year*
(N = 34)

Group 1 –
Recent prescription opioid users who suffered
from an overdose
(N = 444)

Excluded patients moved to Group 2 –
Dependents of prescription opioid users who
suffered from an overdose
(Original N = 51, 84 patients added)
(N = 135)

Excluded patients –
1. Not dependents –
(N = 47)

2. Not temporal–
i.e. prescription in family member does not precede
overdose
(N =23)

Group 2 –
Dependents of prescription opioid users who
suffered from an overdose
(N = 65)

Group 3 –
Others – Neither did the patient nor did any family
member have a prescription before the overdose
(Original N =123, 70 patients added)
(N = 193)

* 1 patient is in 2 groups, a prescription opioid user and the other group. The first overdose was on 07/09/2010 and did not have a prescription associated with it. The next overdose was on 09/29/2011 and had a prescription associated with it.

Figure 3 – Categorizing patients into groups based on source of opioid

Identification of Acute and Chronic Opioid Users

After prescription opioid users were identified, we further classified these patients as acute and chronic users.

Acute and chronic opioid user identification was done by year for patients who had a prescription opioid in the same year they had the overdose.

Patients can be chronic users in one year and acute users in another year. For example, if patients had surgery and were prescribed opioids for four months, they would be classified as chronic users in the year of the surgery. If the same patient was then prescribed an opioid for an acute condition two years later, the patient would be classified as an acute opioid user in that year.

We identified chronic users based on a modification of the 'episode' approach used in previous studies that have focused on long-term opioid therapy.[12,89] Since we were identifying and subsequently classifying patients by year, we modified the definition to suit our study design and data.

We identified patients as chronic opioid users if the total days' supply for all the opioids that a patient was prescribed was greater than 120 days in that year. We assessed days' supply for all opioids so as to account for opioid switching. Based on the variability in literature that has looked at long-term opioid therapy, we decided to identify all patients with 120+ days' supply as chronic opioid users, irrespective of whether the use was continuous or not. [14,69,91–93]

Due to the cross-sectional nature of the data, we could not look back a few months to check if these patients had a prescription in November or December of the previous year since a many patients were not enrolled in the previous year. Therefore, we may have misclassified some chronic users as acute.

Prevalence

Prevalence is defined as the ratio of the number of existing events (old and new) to the total population at risk.

We report the following prevalence estimates –

i. Prevalence of opioid overdose events in the sample population by year

Prevalence of opioid overdoses in the sample population

$$= \frac{\text{Number of overdoses in the sample population in a year}}{\text{Number of people enrolled in the plan in that year}}$$

ii. Prevalence of opioid overdose events by patient group (based on source of opioid)

Prevalence of opioid overdose events in recent prescription opioid users

$$= \frac{\text{Number of overdoses in recent prescription opioid users in a year}}{\text{Number of patients prescribed an opioid in that year}}$$

We also report the following rate for prescription opioid users –

Opioid overdoses per 100,000 opioid prescriptions

$$= \frac{\text{Number of overdoses in recent prescription opioid users in a year}}{\text{Number of opioid prescriptions dispensed that year}}$$

Prevalence of opioid overdose events in family members of prescription opioid users

$$= \frac{\text{Number of overdoses in family members of prescription opioid users in a year}}{\text{Number of family members of prescription opioid users in that year}}$$

Prevalence of opioid overdose events in patients with no source of opioid (others)

$$= \frac{\text{Number of overdoses in these patients in a year}}{\text{Number of "others" enrolled in that year}}$$

The number of others was estimated by subtracting the number of prescription opioid users and family members of prescription opioid users from the number of people enrolled in the plan that year.

iii. <u>Prevalence of opioid overdose events for acute and chronic opioid users</u>

Prevalence of opioid overdose events for acute users

$$= \frac{\text{Number of overdoses in acute opioid users in a year}}{\text{Number of acute opioid users in that year}}$$

Prevalence of opioid overdose events for chronic users

$$= \frac{\text{Number of overdoses in chronic opioid users in a year}}{\text{Number of chronic opioid users in that year}}$$

Sensitivity Analysis

We used sensitivity analysis to determine the extent to which the assumption that individuals who obtain the medication from family members can obtain an old prescription and not necessarily an active one influence the prevalence estimates. We restricted the time from the family member's most recent opioid prescription fill date to the overdose to one year.

Section 3.2 – Results

The results for Specific Aim 1 are presented in this section.

We first describe the prescription opioid users in our sample. This is followed by the prevalence of opioid overdoses in the sample population and the prevalence of opioid overdoses in each of the three groups – recent prescription opioid users, family members of recent prescription opioid users and others.

We then report the prevalence of acute and chronic opioid use and overdoses in acute and chronic opioid users.

Prescription opioid users in the sample population –

There were a total of 398,069 prescription opioid users in the study sample. Majority of the patients prescribed a prescription opioid were in the 18-64 age group. More women were prescribed opioids as compared to men. The average Morphine Equivalent Daily Dose (MEDD) for all prescription opioid users was 81.95 mg/day.

Prescription opioid users in the sample population are described in Table 11.

Table 11 – Demographics for all medication users in the study population

Characteristic	All medication users (N = 667,718)	Prescription opioid users (N = 398,069)	Non-users (N = 269,649)
Age, n (%)			
0-17	172,840 (25.83)	45,681 (11.48)	126,799 (47.02)
18-44	295,226 (44.21)	206,830 (51.96)	88,396 (32.78)
45-65	160,665 (24.06)	115,995 (29.14)	44,670 (16.57)
65 and above	39,347 (5.89)	29,563 (7.43)	9,784 (3.63)
Gender, n (%)			
Female	353,909 (53.00)	223,803 (56.22)	130,106 (48.25)
Male	313,809 (47.00)	174,266 (43.78)	139,543 (51.75)
MEDD, mean (SD)	N/A	81.21 (137.70)	N/A

* Reported only for patients who had complete information

Opioid overdoses in the sample population –

There were a total of 770 opioid overdose events in the period from June 2010 – July 2015 in this population. The prevalence of opioid overdose events by year is reported in Table 12. There was a 119% increase in the prevalence of patients who suffered from an opioid overdose in prescription opioid users from 2011-2014. A graph demonstrating the rise in the rate of opioid overdose events is shown in Table 12.

Table 12 – Prevalence of opioid overdoses in the sample population

Year	2010 (half year)	2011	2012	2013	2014	2015 (half year)	%Δ (2011-2014)*
Number of overdoses	49	91	98	174	224	134	
Number of enrollees	517,351	540,846	530,877	550,170	607,060	664,558	
Prevalence* (per 100,00 enrollees)	-	16.83	18.46	31.63	36.9	-	119.2

Prevalence of opioid overdoses in the sample population = Number of overdoses in the sample population in a year
                                                                                  Number of people enrolled in the plan in that year

*Only computed for complete years
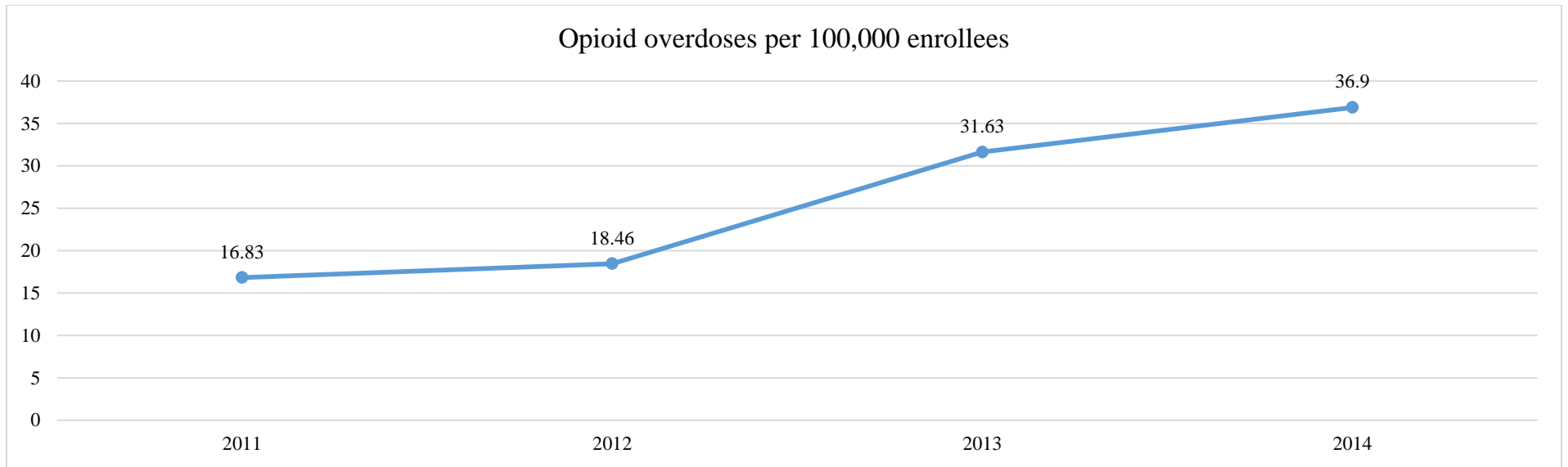
Figure 4– Opioid Overdoses per 100,000 enrollees

Patients who suffered from an overdose by Group –

The three groups into which patients who suffered from an overdose were categorized – recent prescription opioid users who suffered from an overdose, family members of prescription opioid users who suffered from an overdose and others – are described in Table 13.

We also described medication use for the most recent opioid fill before the overdose event for recent prescription opioid users. While women suffered from more overdoses compared to men among the recent prescription opioid users and others, more men suffered from opioid overdoses among family members of recent prescription opioid users. Nearly 19% of non-users (family members and others) who suffered from an overdose were in the 0-17 year age category.

Formulations containing hydrocodone and oxycodone were the most recent fills before an opioid overdose in 68% of prescription opioid users and the mean (SD) MEDD amongst those prescribed an opioid was 127 mg/day (162.94 mg/day).

Table 13 – Characteristics of patients who have suffered from an overdose

Characteristic	Recent Prescription Opioid Users (N = 444)	Family Members (N = 65)	Others (N = 193)
Age, n (%)			
0-17	14 (3.15)	18 (27.69)	30 (15.54)
18-44	204 (45.95)	41 (63.08)	82 (42.49)
45-64	190 (42.79)	6 (9.23)	54 (27.98)
65 and older	36 (8.11)	0 (0)	27 (13.99)
Gender, n (%)			
Male	175 (39.41)	35 (53.85)	73 (37.82)
Female	269 (60.59)	30 (46.15)	120 (62.18)
Cancer patients, n (%)	28 (6.32)	0 (0.00)	4 (2.07)
Concurrent benzodiazepine poisoning, n (%)	8 (1.8)	1 (1.5)	4 (2.07)
Opioid/Formulation containing opioid*, n (%)		N/A	N/A
Buprenorphine	1 (0.23)		
Codeine	18 (4.08)		
Fentanyl	19 (4.31)		
Hydrocodone	124 (28.12)		
Hydromorphone	13 (2.95)		
Methadone	12 (2.72)		
Morphine	38 (8.62)		
Oxycodone	177 (40.14)		
Oxymorphone	5 (1.13)		
Tapentadol	5 (1.13)		
Tramadol	29 (6.58)		
Type of opioid prescription (ER/LA/CR)*, n (%)	47 (10.66)	N/A	N/A
Average MEDD*, mean (SD)	126.94 (162.94)	N/A	N/A

MEDD = Morphine Equivalent Daily Dose; ER = Extended Release; LA = Long Acting; CR = Controlled Release; SD = Standard Deviation

*3 patients did not have complete information about days' supply and quantity dispensed. We have reported these estimates only for patients who had complete information (N=440)

Recent CDC guidelines have stated that physicians should carefully assess benefit and risks when increasing dosage to ≥50 MEDD and should avoid increasing doses to ≥90 MEDD.[94] Therefore, we looked at the number of prescriptions that were in these buckets in our sample. The results are reported in Table 14.

Table 14 – Morphine Equivalent Daily Dose (as categorized by CDC guidelines)[95]

MEDD	Number of prescriptions (%)	Mean	Median	Standard deviation
≤50	1,168,751 (62.66)	25.31	27	12.59
50-89	212,553 (11.40)	63.62	60	9.8
≥90	484,014 (25.95)	226.76	180	208.71

MEDD = Morphine Equivalent Daily Dose;

*These values were estimated for those prescriptions which had complete information only

The mean and median MEDD for acute and chronic users by year is presented in Table 15.

Table 15 – Morphine Equivalent Daily Dose (MEDD) for acute and chronic users

Year	Acute Users	Chronic Users
2011		
Mean (SD)	63.68 (79.99)	95.09 (165.90)
Median	35	40
2012		
Mean (SD)	64.80 (80.12)	98.65 (178.43)
Median	35	40
2013		
Mean (SD)	65.60 (84.19)	103.91 (191.38)
Median	35	40
2014		
Mean (SD)	67.30 (83.94)	106.56 (187.61)
Median	35	40

Some patients in all three groups suffered from more than one overdose during the study period. We report the frequencies and the percentage of people who suffered from more than one overdose by group in Table 16.

Table 16 - Repeated overdoses

	Recent Prescription Opioid Users	Family Members	Others
Number of Patients	444	65	193
Number of Overdoses	493	67	210
Repeated Overdoses	49	2	17
Percentage of people who had a repeat overdose event (%)	11.04	2.94	8.81

Opioid overdoses by group by year –

i. Recent prescription opioid users

The frequencies and prevalence of opioid overdoses in the recent prescription opioid user group is reported in Table 17.

Table 17 – Prevalence of overdoses in recent prescription opioid users

Year	2010 (half year)	2011	2012	2013	2014	2015 (half year)	%Δ (2011-2014)*
Number of overdoses	30	59	68	103	143	90	
Number of patients with an opioid Rx	57,344	106,108	106,942	122,369	139,149	95,442	
Prevalence* (per 100,000 users)	-	55.60	63.59	84.17	102.77	-	84.83

Prevalence = <u>Number of overdoses in recent prescription opioid users in a year</u>
                          Number of patients prescribed an opioid that year

*Only computed for complete years; Rx = prescription

A graph showing the rising prevalence of opioid overdoses in recent prescription opioid user group is shown in Figure 5. We also

report a graph demonstrating the rate of opioid overdoses per 100,000 opioid prescriptions by year in Figure 6.
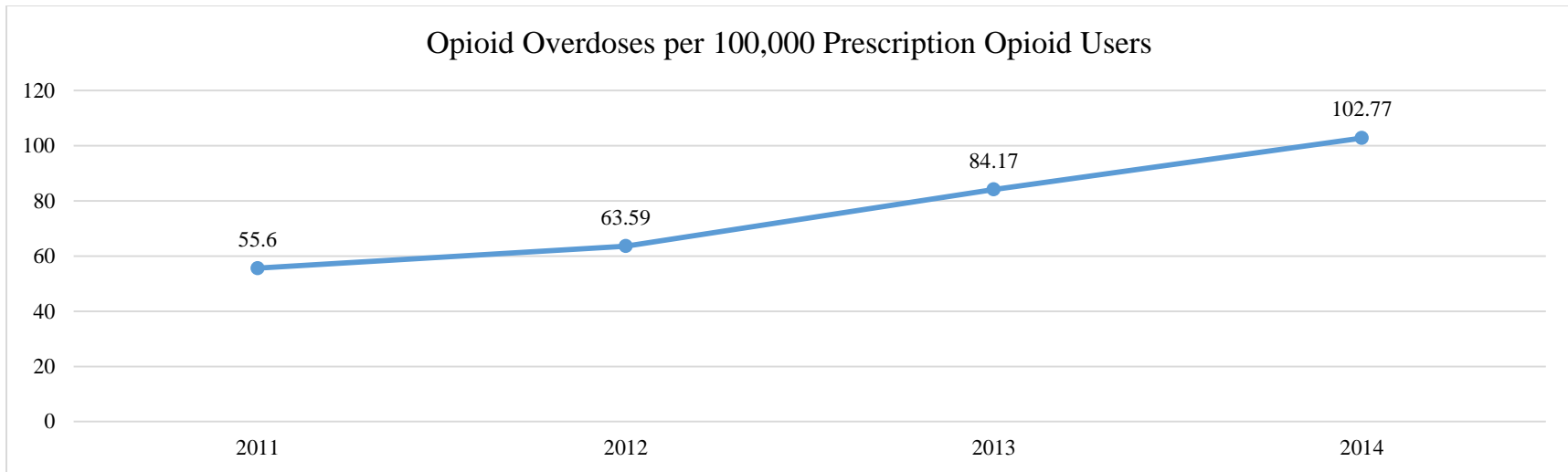
Figure 5 – Opioid overdoses (Prescription Opioid Users) per 100,000 opioid prescription users
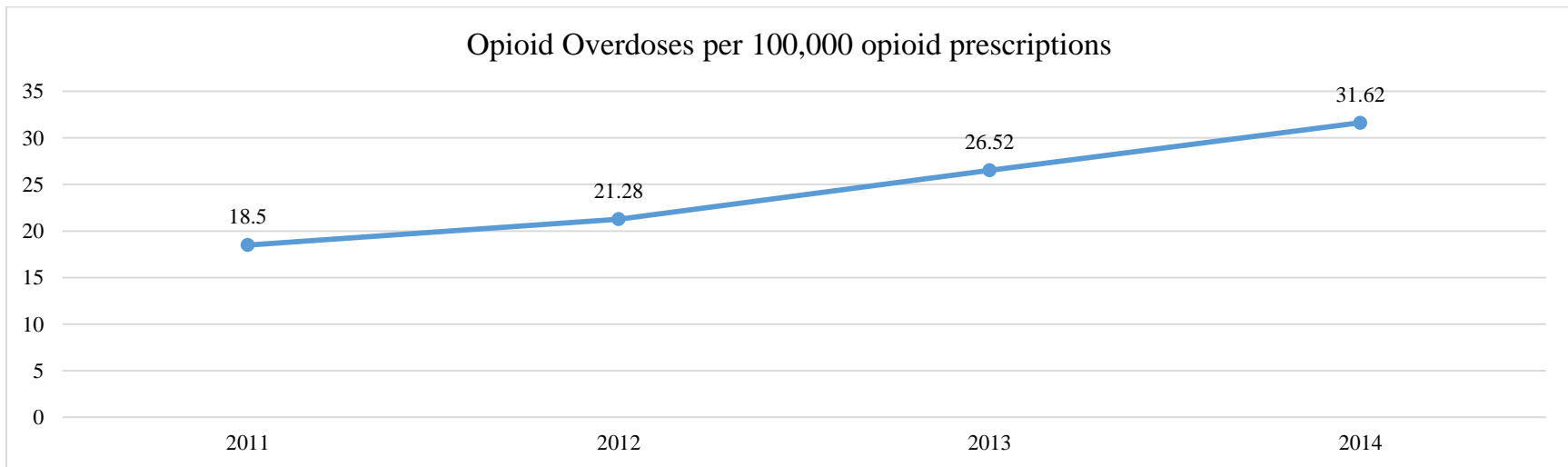
Figure 6 – Opioid Overdoses (Prescription Opioid Users) per 100,000 opioid prescriptions

ii. Family Members of recent prescription opioid users

The frequencies and prevalence of opioid overdoses in the family members of prescription opioid users group is reported in Table 18.

After 2012, the prevalence of overdoses in this group has remained steady.

Table 18 – Prevalence of overdoses in Family Members of Recent Prescription Opioid Users

Year	2010 (half year)	2011	2012	2013	2014	2015 (half year)	%Δ (2011-2014)*
Number of overdoses	3	10	14	12	15	13	
Number of patients with a family member with an opioid Rx	105,011	167,625	166,209	170,314	181,834	133,390	
Prevalence* (per 100,000 users)	-	5.97	8.42	7.05	8.23	-	37.86

Prevalence = Number of overdoses in family members of opioid users in a year / Number of family members of prescription opioid users that year

*Only computed for complete years; Rx = prescription

iii. Others

The frequencies and prevalence of opioid overdoses in the patients who do not have an identifiable source of opioid (others) is

reported in Table 19.

Table 19 – Prevalence of overdoses in others

Year	2010 (half year)	2011	2012	2013	2014	2015 (half year)	%Δ (2011-2014)*
Number of overdoses	16	22	16	59	66	31	
Number of other enrollees	-	267,113	257,726	257,487	286,070	-	
Prevalence* (per 100,000 users)	-	8.24	6.21	22.91	23.07	-	179.98

Prevalence = Number of overdoses in others in a year
             Number of other enrollees that year

*Only computed for complete years

Acute and Chronic Opioid Use –

The proportions of acute and chronic opioid users for each year are reported in Table 20.

Table 20 – Acute and Chronic Users by Year

Year	2011	2012	2013	2014
Acute Users, n (%)	98,088 (92.44)	94,912 (91.94)	111,508 (91.12)	125,286 (90.04)
Chronic Users, n (%)	8,020 (7.56)	8,323 (8.06)	10,861 (8.88)	13,863 (9.96)
*Only included complete years				

Frequencies and prevalence of overdoses in acute and chronic users by year is reported in Table 21.

Table 21 – Number of overdoses in acute and chronic patients by year

i. Acute users

Year	2011	2012	2013	2014	$\%\Delta$ (2011-2014)*
Number of overdoses	43	35	43	63	
Prevalence (per 100,000 acute users)	43.84	36.88	38.56	50.28	14.72

Prevalence of opioid overdoses in acute users = <u>Number of overdoses in acute opioid users in a year</u>
                                                                        Number of acute opioid users in that year

*Only included complete years

ii. Chronic users

Year	2011	2012	2013	2014	%Δ (2011-2014)*
Number of overdoses	15	26	54	69	
Prevalence (per 100,000 chronic users)	187.03	312.39	497.19	497.3	165.89%

Prevalence of opioid overdoses in chronic users = $\dfrac{\text{Number of overdoses in chronic opioid users in a year}}{\text{Number of chronic opioid users in that year}}$

*Only included complete years

In 25 cases, the prescription opioid user received the prescription opioid in a year before the overdose. Since they did not receive a prescription in the year they suffered from an opioid overdose, the user could not be classified as an acute or chronic user in that year and therefore, was not included in the prevalence analysis.

A graph comparing the prevalence of overdoses in acute and chronic users is shown in Figure 7. This graph demonstrates the 165% rise in the prevalence of overdoses in chronic users in the past few years.

While there has not been a steep rise in overdoses in acute opioid users, we can see a slight increase in 2014 as compared to 2012 and 2013.
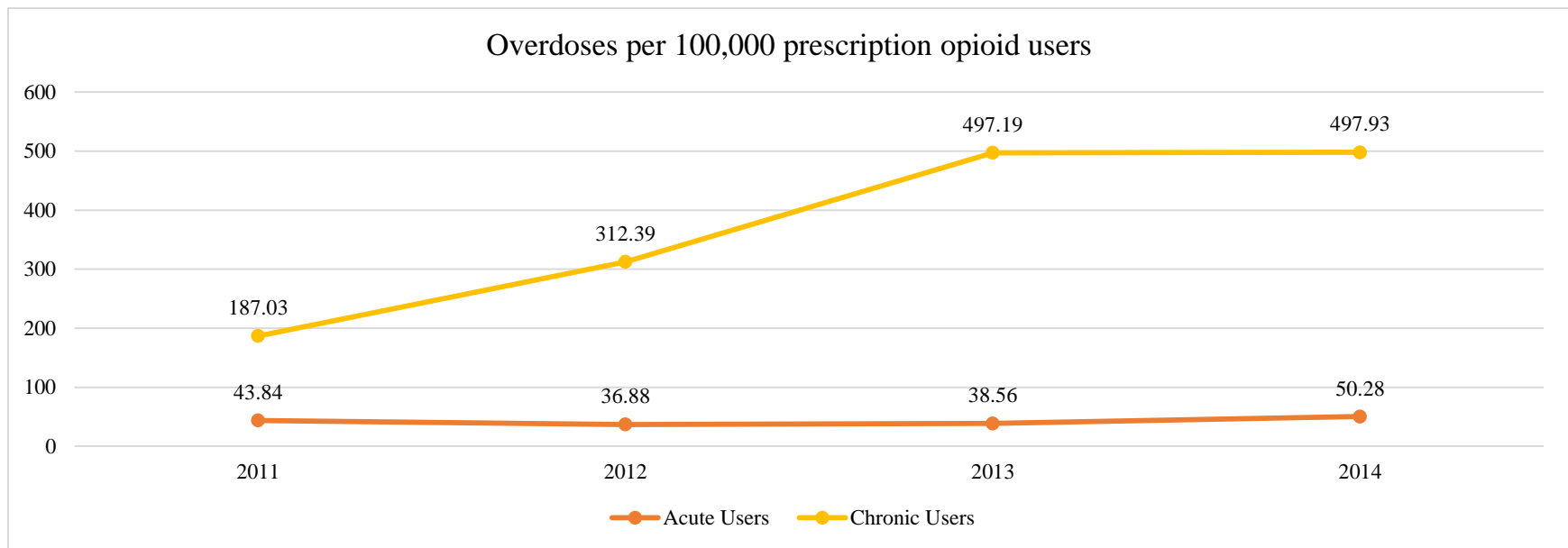
Figure 7 - Overdoses per 100,000 prescription opioid users (acute and chronic respectively) by year

Sensitivity Analysis

The results of a sensitivity analysis restricting the time between the family members' most recent prescription fill date and the overdose to one year are reported in Table 22. From the original estimates, 12 patients who had an overdose from a family member's prescription were moved to the others group because the most recent prescription for the family member was filled more than a year before the overdose.

Table 22 – Characteristics of patients who have suffered from an overdose (revised definition of family members who suffered from an opioid overdose)

Characteristic	Recent Prescription Opioid Users (N = 444)	Family Members (N = 53)	Others (N = 205)
Age, n (%)			
0-17	14 (3.15)	15 (28.30)	33 (16.10)
18-44	204 (45.95)	33 (62.26)	90 (43.90)
45-64	190 (42.79)	5 (9.43)	55 (26.83)
65 and older	36 (8.11)	0 (0.00)	27 (13.17)
Gender, n (%)			
Male	175 (39.41)	30 (56.60)	78 (38.05)
Female	269 (60.59)	23 (43.40)	127 (61.95)

CHAPTER IV

Methods and Results for Specific Aim 2:

Specific Aim 2A: Estimate the incremental cost and resource utilization in prescription opioid users who suffered from an overdose

Specific Aim 2B: Estimate the incremental cost and resource utilization in family members of prescription opioid user and others who suffered from an overdose

Methods
Specific Aim 2A: Estimate the incremental cost and resource utilization in prescription opioid users who suffered from an overdose

This section describes the study methodology used to estimate the cost and resource utilization associated with prescription opioid overdose in prescription opioid users between July 2010 and June 2015.

Study design

The study design was a retrospective data analysis using claims data. For this aim, we used a matched control methodology (propensity score matching) to match cases with controls. We then used an incremental (or econometric approach) to estimate the economic cost of opioid overdose by calculating the difference in mean costs for the two groups.

The index date was defined as the most recent opioid fill before the overdose for cases and the first opioid fill for controls. This date was used to evaluate baseline characteristics for study participants.

The follow-up date was defined as the first opioid overdose for cases. The database was the same as that used for Specific Aim 1, i.e. medical and pharmacy claims data from SelectHealth.

The duration between the most recent opioid prescription and the overdose was calculated for cases and the same duration was then applied to their respective controls from the first fill date to obtain the assigned follow-up date. The study design is explained in and for cases and controls respectively.

Once matched, the participants were followed for one year from the date of the overdose and costs and resource utilization were estimated for this duration.
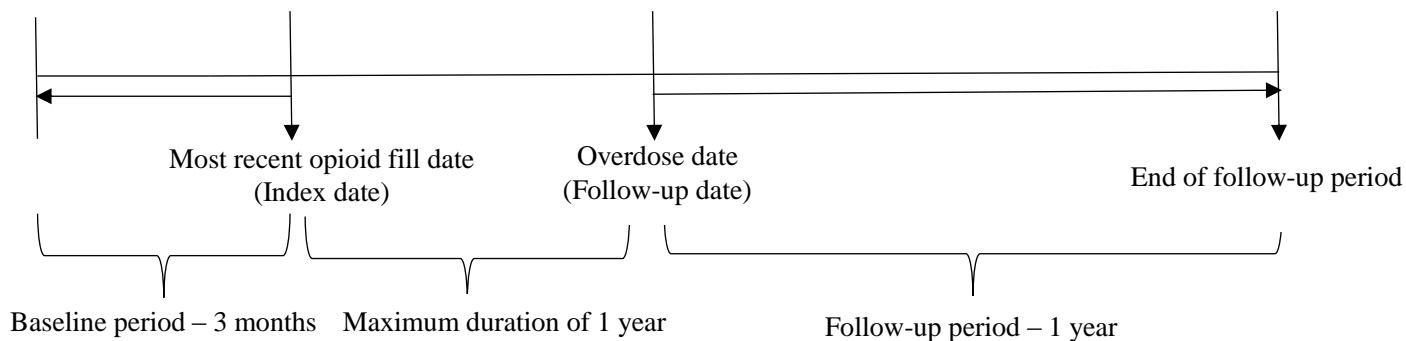
Figure 8 – Study timeline for cases
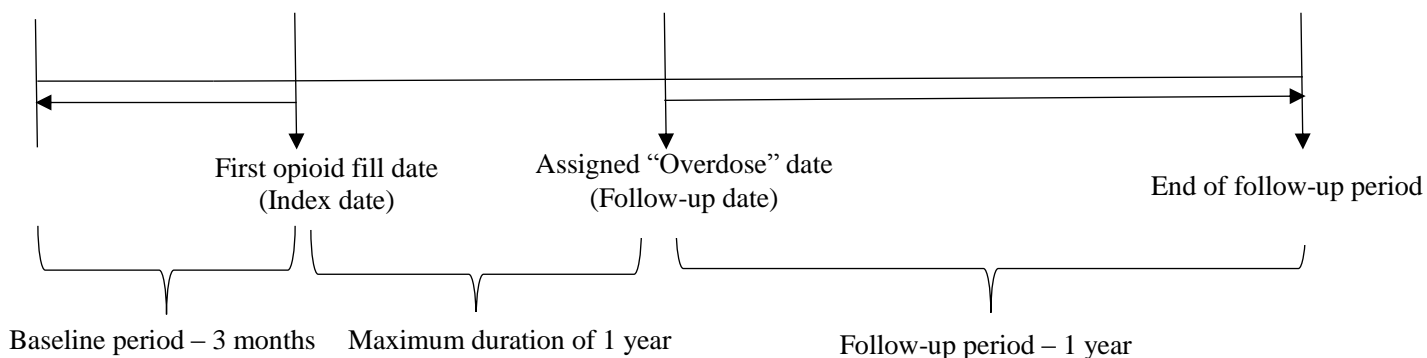
Figure 9 – Study timeline for control

Perspective

The cost estimation and resource utilization were carried out using a payer perspective. Most costs incurred by payers are direct costs and include the cost of medical care provided (for example – ER costs, inpatient costs, drug costs, laboratory costs, medical devices, and professional fees). Payers also have indirect cost in administering their programs for staff, space, utilities, etc.[96] We were only provided with the data to be able to assess the direct cost component for this study. We have captured allowed costs (or reimbursements) for cost estimation in this study.

Sample Selection

The inclusion and exclusion criteria for incremental cost estimation and resource utilization for prescription opioid users is similar to that of the prevalence aim, with four additional exclusion criteria. One, we excluded cancer patients. Since cancer patients are very different from any other population with regards to the severity of sickness and healthcare utilization, we decided to exclude these patients. The ICD-9-CM codes and method used for identification of cancer patients have been included in the appendix (Table A1).

Two, we restricted the sample to patients for whom we had at least 3 months of baseline data because needed baseline resource utilization and comorbidity information for propensity score matching. It is important to note that while we would have preferred a longer baseline period, we had to make a compromise due a greater influx and outflux of patients from year to year than we had anticipated. A baseline period of 3 months was a middle ground to be able to capture baseline characteristics without losing a large portion of our sample.

We also excluded all patients for whom we did not have one year of follow-up to estimate costs. This includes patients who were not enrolled for one year after the follow-up date and patients who had an overdose after July 01, 2014.

Finally, we excluded patients for whom we did not have complete information to calculate the MEDD (Morphine Equivalent Daily Dose). Any patient who did not have complete information on the medication, strength, dosage form, days' supply and quantity dispensed were excluded.

A flowchart explaining the exclusion of patients is shown in Figure 10.
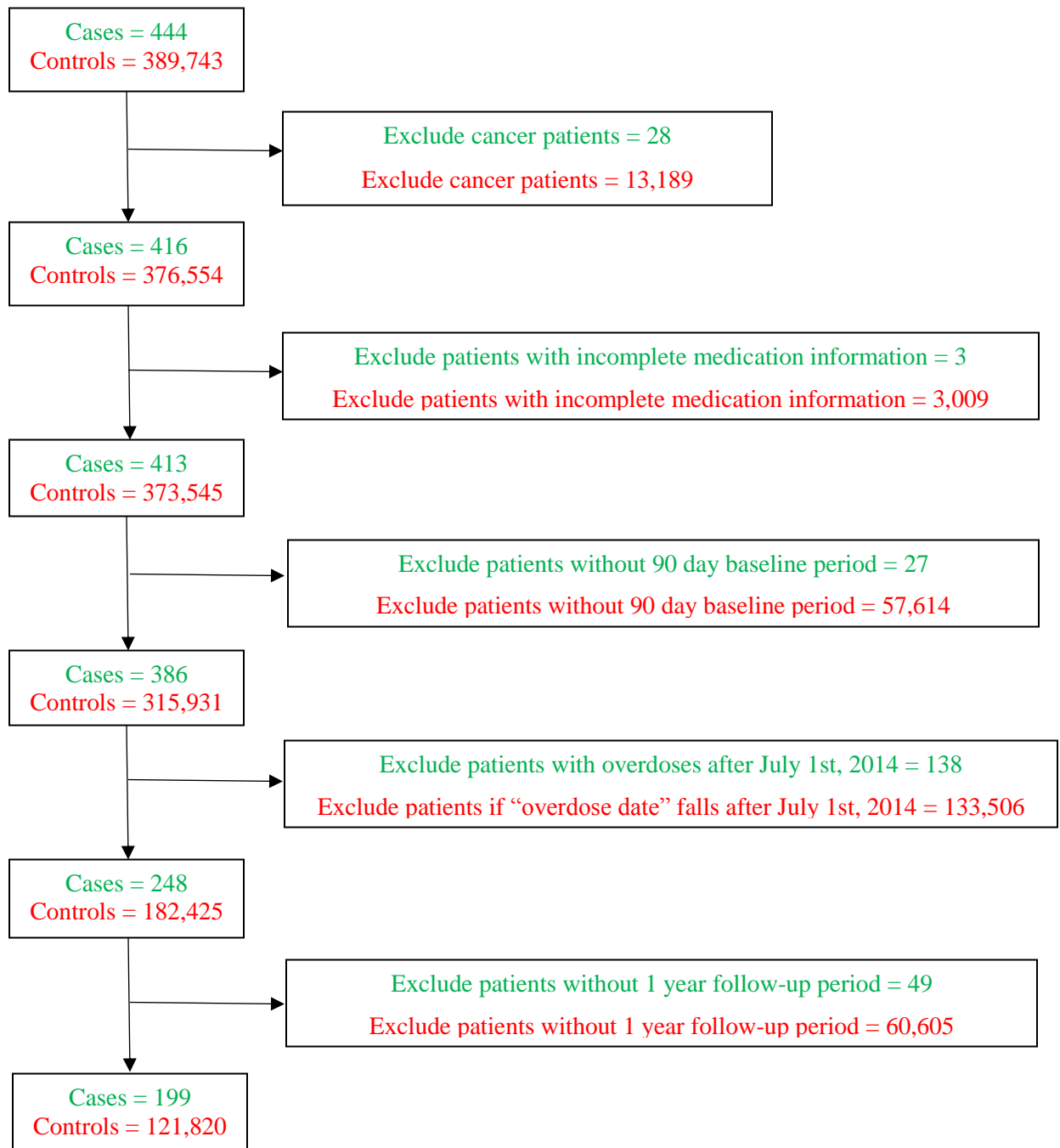
Figure 10 – Sample selection for recent prescription opioid users

Propensity score matching

We performed propensity score matching using the greedy algorithm (also known as nearest neighbor matching). This method allows each case to be matched with the most suitable control available for matching at that point in the matching process and then the case and control are removed from the matching process. We performed a 1:1 match where each case was matched with one control.

One of the key issues in propensity score matching is model specification, i.e. identification of the variables that are included in the model to evaluate a propensity score. We included all the variables that were available to us that have been shown to increase the risk of an overdose in a patient.

Variables used in Propensity Score Matching

Dependent –

Overdose –

An overdose event was identified using the ICD-9-CM codes described in Chapter 3. Overdose is defined as a categorical variable indicating whether or not a patient suffered from an overdose event during the study period.

Independent –

Age –

The age variable was categorized in the following manner – 0-17 years, 18-44 years, 45-64 years and 65 and older.

Sex –

The sex was categorized as male and female.

Comorbidities –

Comorbidity scores are frequently used to reduce potential confounding and account for disease severity in epidemiological research. The Charlson Comorbidity Index (CCI) and the Elixhauser method are commonly used methods in administrative data studies.[97] We used the CCI along with some important variables from the Elixhauser method.

Each condition is assigned a score of 1, 2, 3 or 6 depending on the risk of dying associated with the disease. The scores are then summed and the total score predicts mortality.

A more detailed description of the comorbidities included in the CCI, weights and the ICD-9-CM codes is given in Table 23.

Table 23 – Comorbidities included in CCI, assigned scores and corresponding enhanced ICD-9-CM codes [98,99]

Comorbidity	Score	Enhanced ICD-9-CM
Myocardial infarction	1	410.x, 412.x
Congestive heart failure	1	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x
Peripheral vascular disease	1	093.0, 437.3, 440.x, 441.x, 443.1, 443.2, 443.8, 443.9, 447.1, 557.1, 557.9, V43.4
Cerebrovascular disease	1	362.34, 430.x-438.x
Dementia	1	290.x, 294.1, 331.2
Chronic Pulmonary disease	1	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8
Rheumatic disease	1	446.5, 710.0-710.4, 714.0-714.2, 714.8, 725.x
Peptic ulcer disease	1	531.x-534.x
Mild liver disease	1	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7
Diabetes without chronic complication	2	250.0-250.3
Diabetes with chronic complication	2	250.4, 250.5, 250.6, 250.7
Hemiplegia or paraplegia	2	334.1, 342.x, 343.x, 344.0-3446, 344.9
Renal disease	2	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 5830.0-583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of the skin	2	140.x-172.x, 174.x-195.8, 200.x-208.x, 238.6
Moderate or severe liver disease	3	456.0-456.2, 572.2-572.8
Metastatic solid tumor	6	196.x-199.x
AIDS/HIV	6	042.x-044.x

We chose to include four variables from the Elixhauser comorbidity index – alcohol abuse, drug abuse, psychoses and depression – in the propensity score model as independent variables since these patients are at a higher risk for an overdose.[36] These variables were defined as categorical

variables indicating whether or not a patient was diagnosed with these conditions during the baseline period.

The codes used for these comorbidities are listed in Table 24.

Table 24 – Additional comorbidities included in the propensity score model[98]

Comorbidity	ICD-9-CM codes
Alcohol abuse	265.2, 291.1-291.3, 291.5, 291.8, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0, 57.1-571.3, 980.x, V11.3
Drug abuse	292.x, 304.x, 305.2-305.9, V65.42
Psychoses	293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297.x, 298.x
Depression	296.2, 296.3, 296.5, 300.4, 309.x, 311

Health Care Utilization in the baseline period –

All direct medical care costs were computed for the 3-month baseline period for the cases and controls. These included all medical and pharmacy reimbursements for that period.

Dose –

The MEDD was calculated as described in Chapter III, Section 3.1 (page 53).

Extended Release/Long-Acting Opioid –

If any of the opioid formulations were marked "ER", "XR" or "CR", they were identified as extended release or long-acting formulations. In addition to these formulations, "Exalgo tab

12mg" and "Hydrocodone Polistirex and Chlorpheniramine Polistirex LIQ 10-8/5ML" were identified as extended release formulations.

Benzodiazepine Use –

While there is evidence that the concurrent use of opioids and benzodiazepines increases the risk of opioid overdose[100,101], in this study we are not necessarily looking at the active concurrent use of both medications. Benzodiazepines, like opioids, can be leftover and used at a later date.

Based on this assumption, we identified prescription opioid users who had a prescription for a benzodiazepine before the index date.

Logistic Regression Model –

Logit (Overdose=1) = β_o + β_1 (sex) + β_2 (age) + β_3 (CCI Score) + β_4 (alcohol abuse) + β_5 (drug abuse) + β_6 (psychosis) + β_7 (depression) + β_8 (healthcare cost in the baseline period) + β_9 (MED) + β_{10} (ER/LA/CR formulation) + β_{11} (benzodiazepine use)

Propensity Score Matching diagnostics –

After cases and controls were matched using propensity score matching, we assessed for balance using standardized difference.

Standardized difference for continuous variables was computed using the following formula –

$$d = \frac{(\overline{X_1} - \overline{X_2})}{\sqrt{\frac{s_1^2 + s_2^2}{2}}}$$

Where $\overline{x}_1$ and $\overline{x}_2$ denote the sample mean of a baseline variable and $s_1{}^2$ and $s_2{}^2$ denote the sample

variances in the case and control, respectively.

Standardized difference for categorical variables was computed using the following formula –

$$d = \frac{(\hat{p}_1 - \hat{p}_2)}{\sqrt{\frac{[\hat{p}_1(1-\hat{p}_1) + \hat{p}_2(1-\hat{p}_2)]}{2}}}$$

Where $\hat{p}_1$ and $\hat{p}_2$ denote the proportion of a binary baseline variable in the case and control group,

respectively.

A standardized difference that is less than absolute value 0.1 has been taken to indicate a negligible difference in the mean or proportions of a covariate between the case and control groups. [102]

We plotted the distributions of propensity scores for the cases and controls to visually assess if matching made the distributions alike. [103] We also used the two sample Kolmogorov-Smirnov (K-S) test to assess if the 2 groups were sampled from populations with similar distributions. [104]

Outcome measures

The primary study outcome is the incremental cost over a year between prescription opioid users who have suffered from at least one overdose event and prescription opioid users who have not suffered from an overdose event.

The study outcomes also include all-cause and overdose-specific costs and all-cause and overdose-specific healthcare resource utilization.

Overdose-specific outcomes were identified by claims that had ICD-9-CM codes for opioid overdoses.

The costs were broken down into the following categories based on the place of service variable provided in the dataset (

Table *25*).

Table 25 – Categorization of place of service

Category	Variable
1. Emergency Room (ER)	"EMERGENCY ROOM- HOSPITA"
2. Inpatient	"INPATIENT HOSPITAL", "INPATIENT PSYCHIATRIC F", and "COMPREHENSIVE INPATIENT"
3. Outpatient	"AMBULATORY SURGICAL CEN", "COMMUNITY MENTAL HEALTH", "COMPREHENSIVE OUTPATIEN", "OFFICE", "ON CAMPUS OUTPATIENT HO", "OUTPATIENT HOSPITAL", and "RURAL HEALTH CLINIC"
4. Others	"AMBULANCE-AIR OR WATER", "AMBULANCE-LAND", "END STAGE RENAL DISEASE", "FEDERALLY QUALIFIED HEA", "GROUP HOME", "HOSPICE", "INDEPENDENT LABORATORY", "MOBILE UNIT", "NURSING FACILITY","OTHER UNLISTED FACILITY", "PATIENT'S HOME","PSYCHIATRIC FACILITY PA", "SKILLED NURSING FACILIT", "STATE OR LOCAL PUBLIC H", and "URGENT CARE FACILITY" and "WALK-IN RETAIL HEALTH C"

Statistical Analyses

Baseline covariates were summarized descriptively. Means and standard deviations were reported for continuous variables and frequencies and percentages were reported for categorical variables. Balance was assessed using standardized differences as described above.

Regression was used to model the resource utilization and costs to control for the variables for which propensity score matching process did not achieve adequate balance.

We used a Generalized Linear Model (GLM) with Poisson distribution and a log link function to obtain adjusted incremental resource utilization estimates. For count variables, such as healthcare resource utilization, the Poisson distribution is commonly adopted to represent the distribution. The Poisson distribution is used to represent variables for which the variance is proportional to the mean. [105] If the number of patients with zero resource utilization was greater than 10%, a two-part model was used to obtain the incremental resource utilization. In the first step, a logistic regression model predicted the probability of having healthcare resource use for each patient. [106] The second step used a GLM regression analysis to estimate the adjusted resource utilization for patients who suffered from an overdose and for patients who did not. The adjusted resource utilization was then multiplied by the patient's probability of having healthcare resource utilization. This step adjusted the mean resource utilization estimate downward to account for patients who did not have any healthcare utilization for a specific place of service – for example, ER visits.

We used a Generalized Linear Model (GLM) with gamma distribution and a log link function to obtain adjusted incremental cost estimates. For cost data, such as healthcare costs, the gamma distribution is commonly adopted to represent the distribution due to the skewed nature of costs. The gamma distribution is used to represent variables for which the variance is proportional to

the square of the mean. [105] If the number of patients with zero costs was greater than 10%, a two-part model was used to obtain the incremental cost. In the first step, a logistic regression model predicted the probability of having positive cost for each patient. [107] The second step used a GLM regression analysis to estimate the adjusted cost for patients who suffered from an overdose and for patients who did not. The adjusted cost was then multiplied by the patient's probability of having a positive cost. This step adjusts the mean cost estimate downward to account for patients who had zero costs.

Adjusted healthcare resource utilization and costs during the follow-up period were summarized descriptively. Means and 95% confidence intervals (CIs) were reported for resource utilization estimates and cost estimates.

We also reported the effect sizes for the incremental cost estimates. The effect size was estimated using the following formula[108] –

Effect size = $\dfrac{\text{Mean cost of cases} - \text{Mean cost of controls}}{\text{Standard deviation of the controls}}$

An effect size is a quantitative measure of the difference between two groups and takes into account the sample size of the study.

The standard deviation (SD) of the controls was estimated from the standard error (SE) (refer to the outputs in Appendix) using the formula –

$SD = SE * \sqrt{n}$

A p-value of <0.05 was considered statistically significant.

All costs were adjusted to 2015 U.S. dollars using the medical and prescription component of the

CPI. [109]

All analyses were conducted using SAS version 9.4 and Stata IC 14. [110,111]

Sensitivity Analyses

We used sensitivity analyses to determine the extent to which some of our assumptions influenced our estimates. We conducted three sets of sensitivity analyses –

1. Excluded patients who had costs in the follow-up period greater than $1 million

2. Excluding patients with End Stage Renal Disease (ESRD) – Patients with ESRD need continued treatment and have higher resource utilization.

3. Adopted a 6-month baseline and six-month follow-up period – In order to gauge if a longer baseline period might better control for comorbidities, we conducted a sensitivity analysis with a 6-month baseline period. To account for a reduction in sample size due to a longer baseline period, we decreased the follow-up period to six months instead of one year.

Methods

Specific Aim 2B: Incremental Cost and Resource Utilization in Family Members of Prescription
Opioid User and Others who suffered from an overdose

This section describes the study methodology used to estimate the cost and resource utilization associated with prescription opioid overdose in family members of prescription opioid users and individuals who did not have an opioid prescription themselves and neither did any family member ("others") between July 2010 and June 2015.

We combined the family members of prescription opioid user group and the others group into one category for this aim. Since none of the individuals in either group received their own opioid prescription, these individuals were most likely diverters and/or abusers of the drug. Therefore, these two groups were assumed to have similar type of drug taking behaviors and were collapsed into one category. We will refer to this group as "non-medical users".

The methods in this section are very similar to the methods for Specific Aim 2A with some differences –

1. Identification of the index date for the cases and controls

2. The variables used in the propensity score matching procedure

Only sections that highlight the differences in the methods of the analysis for the non-user group will be presented.

Study design

The study design was a retrospective data analysis using claims data. For this aim, we used a matched control methodology (propensity score matching) to match cases with controls. We then used an incremental (or econometric approach) to estimate the difference in costs for the two groups.

The index date was defined as the date of the overdose for cases and 3 months after the first medical encounter for controls.

Once matched, the participants were followed for one year from the index date and costs and resource utilization were estimated for this duration. The study design is explained in Figure 11 and Figure 12 for cases and controls respectively.
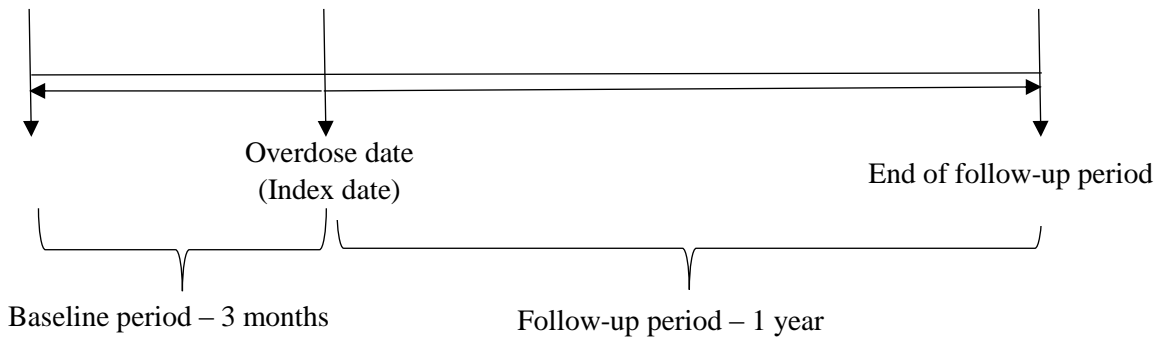
Figure 11 – Study timeline for cases
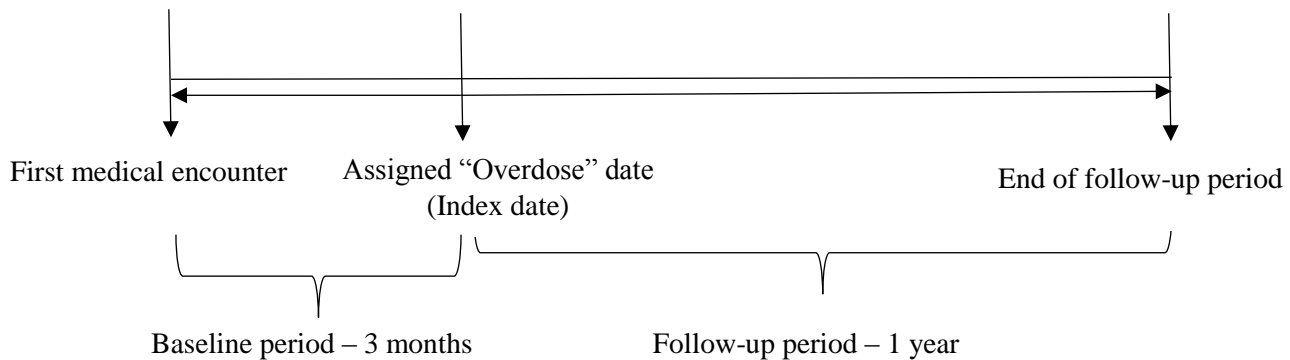
Figure 12 – Study timeline for controls

Sample Selection

The inclusion and exclusion criteria for resource utilization and incremental cost estimation is the same as that of Specific Aim 2A.

A flowchart explaining the exclusion of patients is shown in Figure 13.
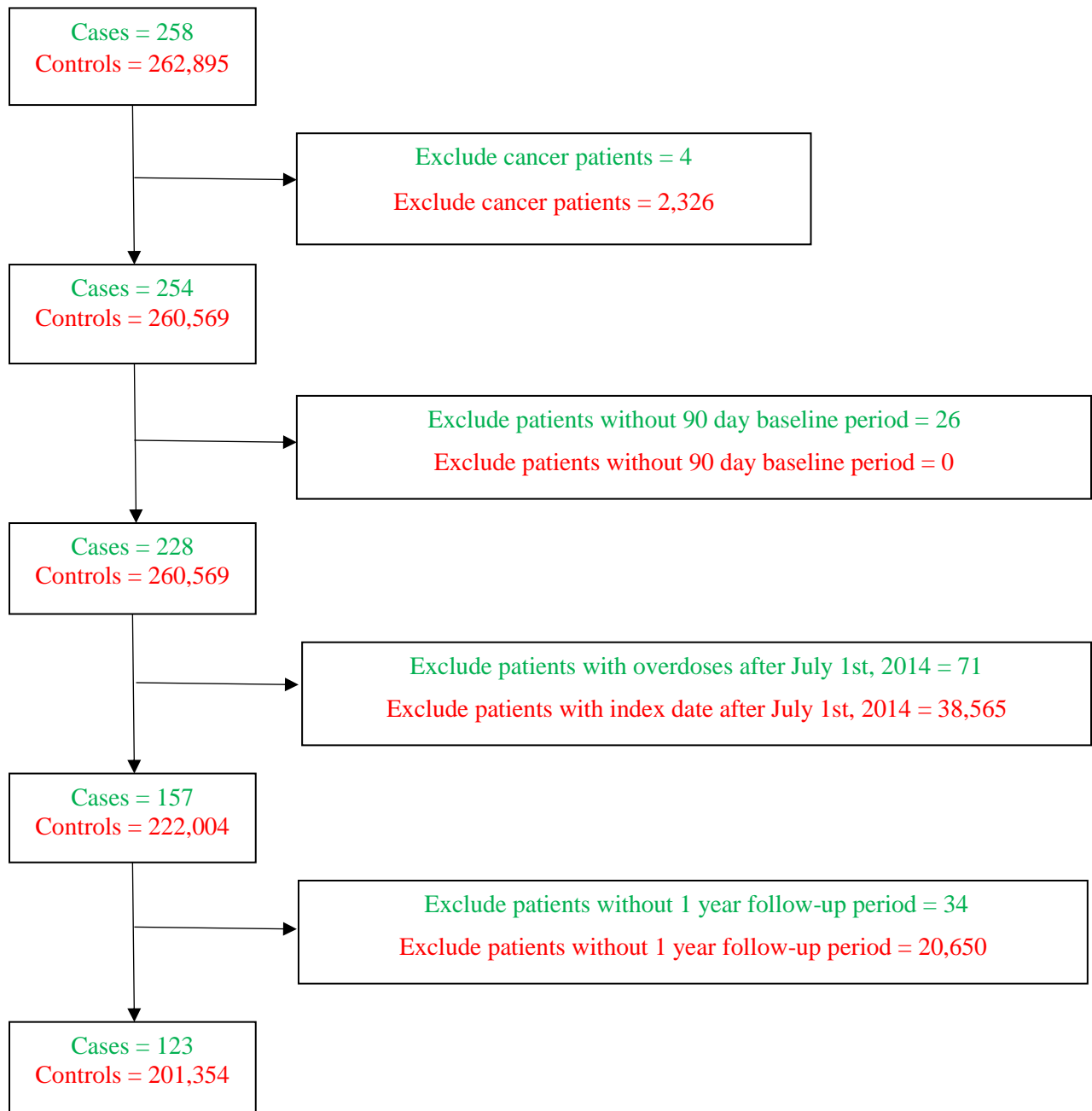
Figure 13 – Sample selection for non-medical users

Propensity score matching

Variables used in Propensity Score Matching –

The variables used in this propensity score match are demographics (age, sex), comorbidities at baseline, and healthcare resource utilization in the baseline period.

The variables have been categorized or computed using the same method used for the prescription opioid users.

One important difference between the propensity score matching between the prescription opioid users and non-users is that we could not account for the opioid-specific variables (MED and whether the opioid was an extended release formulation) since we do not have information about the opioid that caused the overdose in these patients.

Logistic Regression Model –

Logit (Overdose=1) = $\beta_o + \beta_1$ (sex) + β_2 (age) + β_3 (CCI Score) + β_4 (alcohol abuse) + β_5 (drug abuse) + β_6 (psychosis) + β_7 (depression) + β_8 (healthcare cost in the baseline period)

The methods used for propensity score matching diagnostics in Specific Aim 2A are applied here as well.

Sensitivity Analyses

We conducted the same set of sensitivity analyses as listed for Specific Aim 2A –

1. Excluded patients who had costs in the follow-up period greater than $1 million

2. Excluded patients with End Stage Renal Disease (ESRD)

3. Adopted a 6-month baseline and 6-month follow-up period

Human Subjects Protection and Data Privacy

SelectHealth data was de-identified and used encrypted member IDs. Access to the dataset was restricted to individuals listed on the protocol. The data were maintained in a password-protected environment on the VCU server. The study proposal was submitted to the Institutional Review Board (IRB) at Virginia Commonwealth University for an exemption 45 CFR 46.404. The approval number was HM20004383.

Results

Specific Aim 2A: Incremental Cost and Resource Utilization for Prescription Opioid Users who suffered from an overdose

The results of the propensity score matching are reported followed by the incremental resource utilization and cost estimates between prescription opioid users who suffered from an overdose event and prescription opioid users who did not.

Propensity score matching diagnostics –

The distribution of the computed propensity scores before and after matching are shown in and 15 respectively.

The K-S statistic before matching was 7.88, p-value<0.0001 and after matching was 0.201, p-value = 1.000. This indicates that the propensity scores have similar distributions for those who suffered from an overdose and those who did not after matching.

The baseline characteristics before and after propensity score are presented in Table 26 and Table 27 respectively. The mean propensity scores before and after matching are also presented.
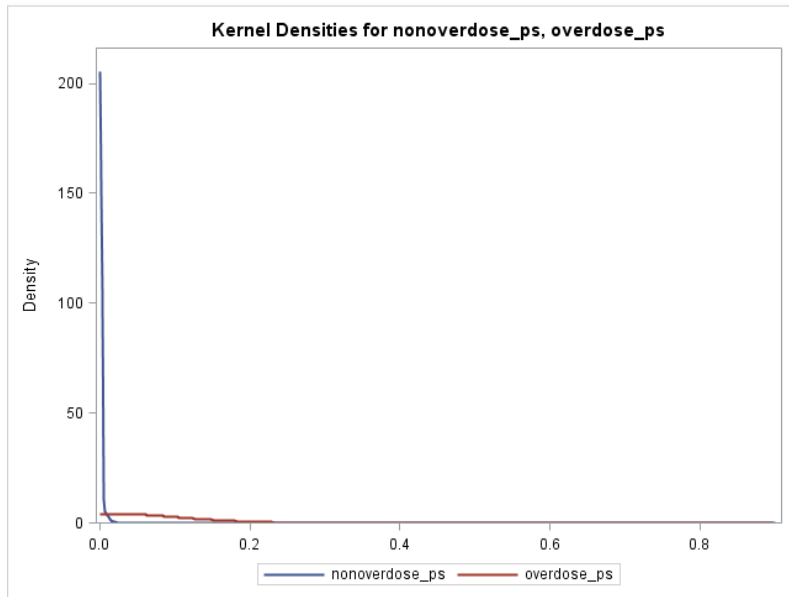
Figure 14 – Propensity score distribution before matching
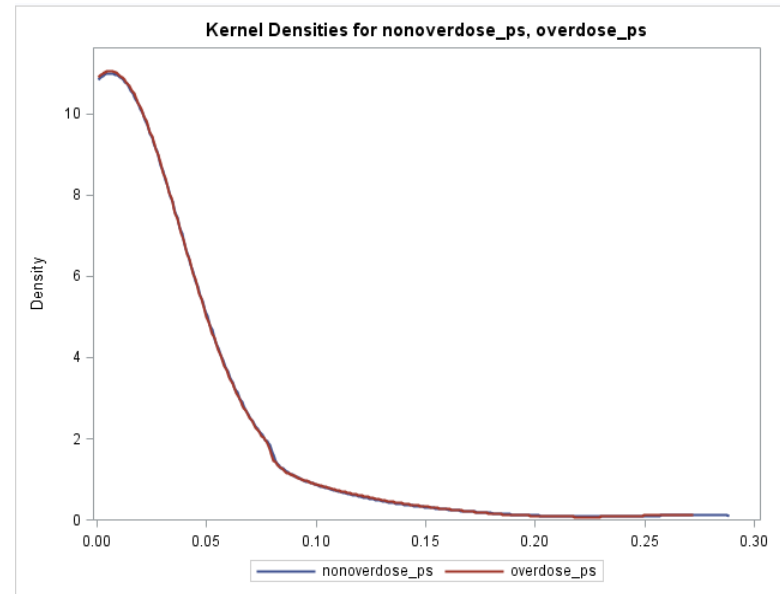
Figure 15 – Propensity Score distribution after matching

Table 26 - Baseline characteristics for recent prescription opioid users before matching

Characteristics	Overdose cohort (N = 199)	Control cohort (N = 121,820)	ASD
Age group (years), n (%)			
0-17	4 (2.01)	13,984 (11.48)	0.385
18-44	104 (52.26)	64,659 (53.08)	0.016
45-64	79 (39.70)	37,246 (30.57)	0.192
65 and above	12 (6.03)	5,931 (4.87)	0.051
Sex, n (%)			
Female	123 (61.81)	67,525 (55.43)	0.13
Male	76 (38.19)	54,295 (44.57)	0.13
CCI Score, mean (SD)	0.34 (0.81)	0.07 (0.34)	0.435
Other comorbidities, n (%)			
Alcohol abuse	3 (1.51)	121 (0.10)	0.158
Drug abuse	9 (4.52)	316 (0.26)	0.282
Psychoses	8 (4.02)	130 (0.11)	0.278
Depression	39 (19.60)	3,362 (2.76)	0.555
MEDD, mean (SD)	110.1 (140.8)	54.5 (69.81)	0.5
ER/XR/CR, n (%)	23 (11.62)	857 (0.70)	0.466
Benzodiazepine use, n (%)	100 (50.25)	24,249 (19.91)	0.671
Baseline healthcare costs, mean (SD)	16,576 (42,925)	2,931 (15,540)	0.423
Propensity score, mean (SD)*	0.02 (0.06)	0.002 (0.007)	

ASD = Absolute Standardized Differences; CCI = Charlson Comorbidity Score; CR = Controlled Release; ER = Extended Release; MEDD = Morphine Equivalent Daily Dose XR = Extended Release; *This variable was not included in the model

Table 27 – Baseline characteristics for recent prescription opioid users after matching

Characteristics	Overdose cohort (N = 198)	Control cohort (N = 198)	ASD
Age group (years), n (%)			
0-17	4 (2.02)	11 (5.56)	0.186
18-44	104 (52.53)	78 (39.39)	0.266
45-64	78 (39.39)	87 (43.94)	0.092
65 and above	12 (6.06)	22 (11.11)	0.181
Sex, n (%)			
Female	122 (61.62)	129 (65.15)	0.073
Male	76 (38.38)	69 (34.85)	0.073
CCI Score, mean (SD)	0.33 (0.81)	0.39 (0.96)	0.068
Other comorbidities, n (%)			
Alcohol abuse	3 (1.52)	4 (2.02)	0.038
Drug abuse	9 (4.55)	13 (6.57)	0.089
Psychoses	7 (3.54)	6 (3.03)	0.029
Depression	39 (19.70)	38 (19.19)	0.013
MEDD, mean (SD)	110.55 (141.09)	105.82 (152.03)	0.032
ER/XR/CR, n (%)	22 (8.59)	17 (11.59)	0.099
Benzodiazepine use, n (%)	99 (50.00)	99 (50.00)	0
Baseline healthcare costs, mean (SD)	16,634 (43,027)	14,867 (74,261)	0.029
Propensity score, mean (SD)*	0.02 (0.04)	0.02 (0.04)	

ASD = Absolute Standardized Differences; CCI = Charlson Comorbidity Score; CR = Controlled Release; ER = Extended Release; MEDD = Morphine Equivalent Daily Dose XR = Extended Release; *This variable was not included in the model

The baseline characteristics before matching were significantly different for all variables.

After propensity score matching, the two groups matched on all variables except age (Table 27). To account for this imbalance between the two groups, a regression analysis was performed and age was included in the model to obtain adjusted incremental costs and resource utilization.

Extreme values

As part of the cost analysis, allowed costs with a value of '0' were observed in the dataset. A claim could have been paid for by another payer, bundled with another claim or payment for that claim could have been denied. Therefore, we used all values as they were and did not impute costs for claims with a value of '0'.

Additionally, there were patients with costs in the follow-up period greater than $1,000,000. When the healthcare costs of these patients were examined closely, we did not find any duplicate claims on the same day for the same diagnosis. The allowed costs were per claim and per diagnoses. However, we saw examples of recurring costs for a month in the outpatient setting, high charges for claims for seemingly benign conditions like nausea and claims that were identical except that some had a cost value and some had a zero value. We tried to get more information about these claims, but were unable to and used them as they were for our analysis. However, we excluded patients with costs in the follow-up period greater than $1,000,000 in a sensitivity analysis.

The proportion of patients who had a medical encounter is categorized by place of service and presented in Table 28. Unadjusted estimates for healthcare utilization by place of service for prescription opioid users is presented in Table 29.

Table 28 – Healthcare resource utilization by prescription opioid users with and without at least one overdose event in the follow-up period in a matched population (Number of patients)

Variable	Cases	Controls	p-value
Patients, n	198	198	
Resource utilization, n (%)			
All-cause inpatient visits	135 (68.18)	32 (16.16)	<0.0001
All-cause ER visits	183 (92.42)	62 (31.31)	<0.0001
All-cause outpatient visits	194 (97.98)	190 (95.96)	0.2410
All-cause other visits	177 (89.40)	126 (63.64)	<0.0001
Overdose-specific inpatient visits *	79 (39.90)	N/A	N/A
Overdose-specific ER visits*	138 (69.70)	N/A	N/A
Overdose-specific outpatient visits*	26 (13.13)	N/A	N/A
Overdose-specific other visits*	8 (4.04)	N/A	N/A
*Are not mutually exclusive			

Table 29 – Unadjusted healthcare resource utilization for prescription opioid users with and without at least one overdose event in the follow-up period in a matched population (Number of visits)

Resource utilization, mean (SD)	Cases	Controls	Difference	p-value
Patients, n	198	198		
All-cause inpatient visits	1.60 (2.57)	0.27 (0.39)	1.33 (2.71)	<0.0001

All-cause ER visits	3.52 (4.46)	0.85 (3.38)	2.67 (5.69)	<0.0001
All-cause outpatient visits	19.55 (17.90)	13.11 (14.36)	6.44 (21.95)	<0.0001
All-cause other visits	9.39 (19.28)	3.88 (9.31)	5.51 (20.55)	0.0002
Overdose-specific inpatient visits	0.43 (0.57)	N/A	N/A	N/A
Overdose-specific ER visits	0.87 (0.71)	N/A	N/A	N/A
Overdose-specific outpatient visits	0.16 (0.44)	N/A	N/A	N/A
Overdose-specific other visits	0.07 (0.53)	N/A	N/A	N/A

Unadjusted healthcare costs for prescription opioid users by place of service are presented in Table 30.

Table 30 – Unadjusted healthcare costs for prescription opioid users with and without at least one overdose event in the follow-up period in a matched population

Mean health care cost, US$ (95% CI)	Cases	Controls	Cost difference	p-value
All-cause health care costs	76,811 (50,637, 102,984)	16,545 (11,991, 21,098)	60,266 (33,646, 86,886)	<0.0001
All-cause inpatient	33,460 (18,392, 48,528)	4,188 (1,820, 6,557)	29,272 (14,118, 44,426)	0.0002
All-cause ER	5,846 (4,774, 6,917)	1,695 (786, 2,604)	4,151 (2,706, 5,595)	<0.0001
All-cause outpatient	24,398 (7,051, 41,745)	6,233 (4,530, 7,937)	18,165 (628, 35,702)	0.0424
All-cause others	9,635 (4,397, 14,872)	2,022 (794, 3,250)	7,613 (2,216, 13,010)	0.0059
Pharmacy costs	3,473 (2,859, 4,086)	2,407 (1,854, 2,960)	1,066 (280, 1,858)	0.0086
Overdose-specific inpatient	10,491 (1,450, 19,532)	N/A	N/A	N/A
Overdose-specific ER	1,498 (1,117, 1,879)	N/A	N/A	N/A
Overdose-specific outpatient	58 (-35, 151)	N/A	N/A	N/A
Overdose-specific others	64 (15, 112)	N/A	N/A	N/A

Incremental resource utilization

Adjusted healthcare resource utilization for recent prescription opioid users is given in Table 31. Healthcare resource utilization was different for every category of place of service between cases and controls groups during the follow-up period. This indicates that including the overdose event, the cases had greater healthcare resource utilization as compared to the controls. (All p-values <0.05).

Table 31 – Adjusted healthcare resource utilization for recent prescription opioid users with and without at least one overdose event in the follow-up period in a matched population

Resource utilization, Mean (95% CI)	Cases	Controls	Adjusted difference in resource utilization (95% CI)	p-value
Patients, n	198	198		
All-cause inpatient visits	1.62 (1.39, 1.86)	0.27 (0.16, 0.38)	1.36 (1.10, 1.62)	<0.0001
All-cause ER visits	3.43 (3.14, 3.72)	0.89 (0.66, 1.12)	2.54 (2.17, 2.91)	<0.0001
All-cause outpatient visits	19.67 (19.04, 20.29)	13.02 (12.52, 13.53)	6.64 (5.84, 7.45)	<0.0001
All-cause other visits	9.89 (9.28, 10.51)	3.67 (3.23, 4.10)	6.23 (5.48, 6.98)	<0.0001
Overdose-specific inpatient visits	0.43 (0.35, 0.51)	N/A	N/A	N/A
Overdose-specific ER visits	0.87 (0.77, 0.97)	N/A	N/A	N/A
Overdose-specific outpatient visits	0.16 (0.1. 0.22)	N/A	N/A	N/A
Overdose-specific other visits	0.07 (-0.003, 0.14)	N/A	N/A	N/A

The incremental difference between all cause healthcare costs for recent prescription opioid users who suffered from an overdose and those who did not was estimated to be $65,277 (P-value <0.05) (Table 32). The cost difference for all places of service except for others were significantly different between the two groups. Overdose-specific healthcare costs were estimated to be $12,111. The Stata outputs for incremental cost and resource utilization estimation are presented in Appendix B. The effect size of the incremental all-cause healthcare costs was estimated to be 1.37. According to Cohen's interpretation of effect size, an effect size greater than 0.8 represents a large effect size.

Table 32 – Adjusted healthcare costs for recent prescription opioid users with and without at least one overdose event in the follow-up period in a matched population

Mean health care cost, US$ (SD)	Cases	Controls	Cost difference (95% CI)	p-value
All-cause health care costs	81,007 (55,539, 106,475)	15,730 (11,031, 20,429)	65,277 (39,440, 91,114)	<0.0001
All-cause inpatient	34,336 (19,003, 49,669)	3,925 (347, 7503)	30,411 (14,583, 46,240)	<0.0001
All-cause ER	5,726 (4,515, 6,938)	1,731 (1,012, 2,450)	3,996 (2,587, 5,404)	<0.0001
All-cause outpatient	22,234 (11,955, 32,513)	6,905 (3,379, 10,431)	15,329 (4,402, 26,257)	0.006
All-cause others	11,166 (3,491, 18,842)	1,736 (501, 2,971)	9,431 (1,992, 16,869)	0.013
Pharmacy costs	3,494 (2,702, 4,286)	2,393 (1,853, 2,932)	1,101 (160, 2,042)	0.022
Overdose-specific inpatient	10,491 (1,450, 19,532)	N/A	10,491 (1,450, 19,532)	
Overdose-specific ER	1,498 (1,117, 1,879)	N/A	1,498 (1,117, 1,879)	
Overdose-specific outpatient	58 (-35, 151)	N/A	58 (-35, 151)	
Overdose-specific others	64 (15, 112)	N/A	64 (15, 112)	

Table 33 and Table 34 list the five diagnoses with the highest per patient cost for those who suffered from an overdose and those who did not. The overdose group has two diagnoses of drug dependence which are associated with drug abuse and one diagnosis for amphetamine abuse, unlike the patients who did not suffer from an overdose.

Table 33 – Diagnoses with the highest cost in the follow-up year for prescription opioid users who suffered from an overdose

Diagnosis description	ICD-9-CM code	Cost per patient ($)
1. Combinations of drug dependence excluding opioid type drug, unspecified	304.80	416,927
2. Amphetamine or related acting sympathomimetic abuse, continuous	305.71	268,587
3. Autoimmune disease, not elsewhere classified	279.49	228,975
4. Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled	250.70	227,916
5. Opioid type dependence, unspecified use	304.00	122,174

Table 34 – Diagnoses with the highest cost in the follow-up year for prescription opioid users who did not suffer from an overdose.

Diagnosis description	ICD-9-CM code	Cost per patient ($)
1. Bulimia	307.51	95,123
2. Other pneumothorax and air leak	512.8	86,474
3. Mechanical complication of other vascular device, implant, and graft	996.1	73,625
4. Coronary atherosclerosis of native coronary artery	414.01	62,685
5. Dissecting aortic aneurysm of unspecified site	441.00	62,416

Table 35 and Table 36 list the most commonly occurring diagnoses for patients who suffered from an overdose (excluding overdoses) and patients who did not. In patients who suffered from an overdose, two codes are for pain and the other three codes represent overdoses due to other substances, depression and alteration of consciousness. The patients who did not have an overdose suffer from depression, but no other diagnoses indicate risk factors for an overdose.

Table 35 - Most frequent diagnoses in the follow-up year for prescription opioid users who suffered from an overdose, excluding overdose diagnoses

Diagnosis description	ICD-9-CM code	Number of patients
1. Major depressive affective disorder, recurrent episode, moderate	296.32	88
2. Poisoning by unspecified drug or medicinal substances	977.9	80
3. Alteration of consciousness, other	780.09	50
4. Pain in limb	729.5	47
5. Abdominal pain, unspecified site	789.00	46

Table 36 – Most frequent diagnoses in the follow-up year for prescription opioid users who did not suffer from an overdose

Diagnosis description	ICD-9-CM code	Number of patients
1. Need for other prophylactic vaccination and inoculation against single diseases	V05.8	44
2. Examination of eyes and vision	V72.0	34
3. Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled	250.00	33
4. Major depressive affective disorder, recurrent episode, mild	296.31	29
5. Other malaise and fatigue	780.79	27

Cost Curve

The costs on the day of the overdose (time point 0) and subsequently after the overdose in prescription opioid users are shown in Figure 16.
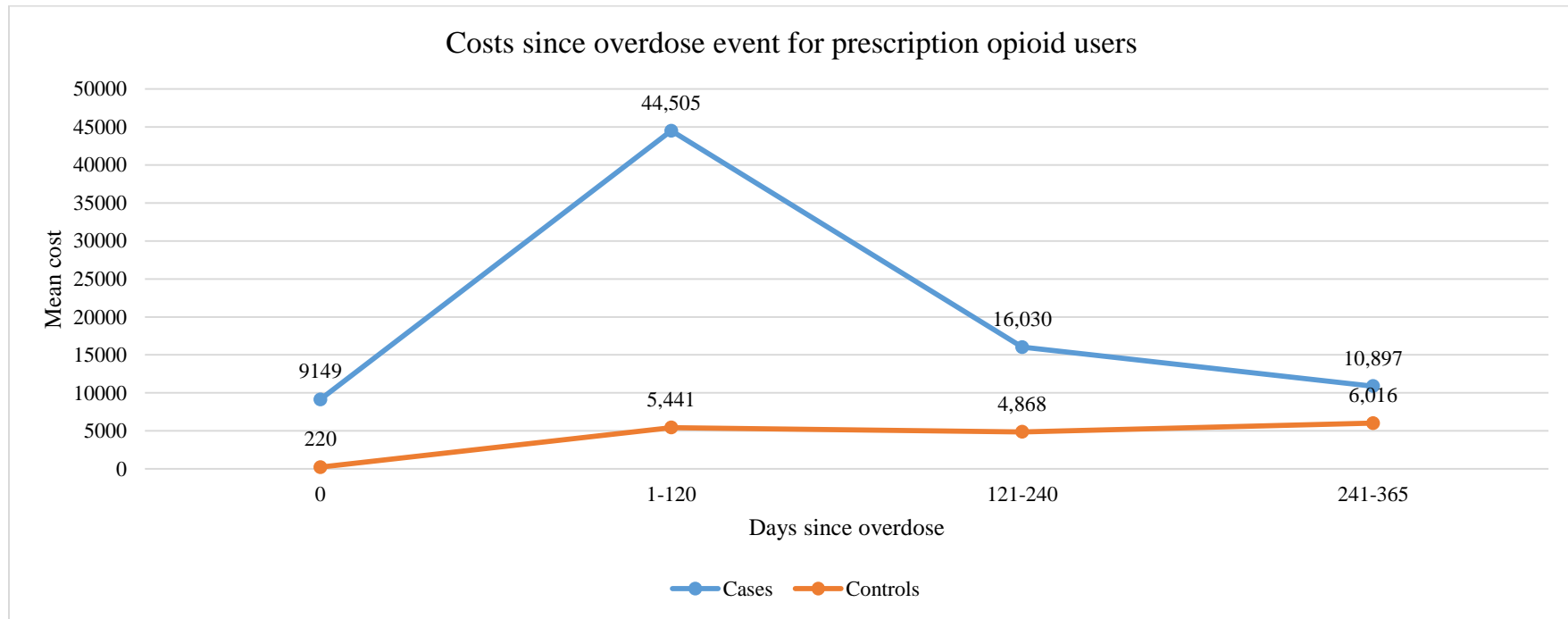
Figure 16 – Costs since overdose event for prescription opioid users (unadjusted)

Sensitivity Analyses

1. Exclude costs greater than $1 million

In the prescription opioid user group, three patients (all cases) had costs greater than $1 million. We assessed for balance after excluding the three patients and balance was achieved for all variables except for age. GLM was used to obtain adjusted estimates. The results are presented in Table 37.

Table 37 – Sensitivity Analysis – Adjusted healthcare costs for recent prescription opioid users with and without at least one overdose event in the follow-up period in a matched population after excluding patients with costs greater than $1 million during the follow-up period

Mean health care cost, US$ (95% CI)	Cases (N= 195)	Controls (N= 198)	Cost difference (95% CI)	p-value
All-cause health care costs	63,412 (44,646, 82,178)	15,693 (11,322, 20,064)	47,720 (28,573, 66,866)	<0.0001
All-cause inpatient	30,152 (17,061, 43,242)	3,924 (438, 7,409)	26,288 (12,576, 39,881)	<0.0001
All-cause ER	5,758 (4,527, 6,989)	1,731 (1,011, 2,450)	4,027 (2,602, 5,453)	<0.0001
All-cause outpatient	12,817 (7,905, 17,730)	6,189 (3,852, 8,526)	6,628 (1,173, 12,084)	0.017
All-cause others	9,486 (2,991, 15,981)	1,755 (504, 3,007)	7,731 (1,483, 13,979)	0.015
Pharmacy costs	3,502 (2,735, 4,270)	2,400 (1,863, 2,937)	1,103 (178, 2,027)	0.019
Overdose-specific inpatient	10,221 (1,190, 19,253)	N/A	N/A	N/A
Overdose-specific ER	1,467 (1,087, 1,848)	N/A	N/A	N/A
Overdose-specific outpatient	58 (-35, 151)	N/A	N/A	N/A
Overdose-specific others	64 (15, 112)	N/A	N/A	N/A

2. Exclude patients with End Stage Renal Disease (ESRD)

In the prescription opioid user group, two patients (1 case, 1 control) had claims for ESRD in the follow-up period. We assessed for balance after excluding the two patients and balance was achieved for all variables except for age. GLM was used to obtain adjusted estimates. The results are presented in Table 38.

Table 38 – Sensitivity Analysis – Adjusted healthcare costs for recent prescription opioid users with and without at least one overdose event in the follow-up period in a matched population after excluding patients with ESRD

Mean health care cost, US$ (95% CI)	Cases (N=197)	Controls (N=197)	Cost difference (95% CI)	p-value
All-cause health care costs	74,415 (51,372, 97,457)	15,823 (11,125, 20,521)	58,592 (35,108, 82,076)	<0.0001
All-cause inpatient	29,970 (17,007, 42,930)	3,939 (439, 7,438)	26,030 (12,501, 39,560)	<0.0001
All-cause ER	5,731 (4,505, 6,957)	1,691 (979, 2,405)	4,040 (2,623, 5,457)	<0.0001
All-cause outpatient	22,162 (11,846, 32,477)	6,939 (3,360, 10,517)	15,223 (4,240, 26,206)	0.007
All-cause others	9,280 (2934, 15,625)	1,721 (479, 2,963)	7,559 (1,451, 13,667)	0.015
Pharmacy costs	3,495 (2,733, 4,257)	2,407 (1,869, 2,945)	1,088 (168, 2,008)	0.020
Overdose-specific inpatient	10,273 (1,196, 19,350)	N/A	N/A	N/A
Overdose-specific ER	1,505 (1,123, 1,888)	N/A	N/A	N/A
Overdose-specific outpatient	58 (-35, 152)	N/A	N/A	N/A
Overdose-specific others	64 (15, 113)	N/A	N/A	N/A

3. Adopted 6-month baseline and 6-month follow-up periods

We obtained a sample of 259 cases and 109,988 controls after assessing for eligibility and obtained 257 matched pairs after propensity score matching. This cohort of prescription opioid users achieved balance for all variables. We used a paired t-test to obtain incremental cost estimates. The results of this analysis are presented in Table 39.

Table 39 – Sensitivity Analysis – Adjusted healthcare costs for recent prescription opioid users with and without at least one overdose event in a 6-month follow-up period in a matched population

Mean health care cost, US$ (95% CI)	Cases (N=257)	Controls (N=257)	Cost difference (95% CI)	p-value
All-cause health care costs	55,629 (36,901, 74,356)	14,181 (1,021, 27,341)	41,448 (18,355, 64,541)	0.0005
All-cause inpatient	25,856 (14,735, 36,977)	2,110 (877, 3,343)	23,746 (12,523, 34,968)	<0.0001
All-cause ER	5,035 (3,692, 6,378)	529 (262, 797)	4,503 (3,129, 5,882)	<0.0001
All-cause outpatient	15,994 (2,870, 29,118)	3,020 (2,093, 3,946)	12,975 (-204, 26,153)	0.0536
All-cause others	6,926 (3,577, 10,274)	7,211 (-5,825, 20,247)	-286 (-13,779, 13,208)	0.9668
Pharmacy costs	1,819 (1,490, 2,148)	1,311 (934, 1,687)	508 (6, 1,010)	0.0474
Overdose-specific inpatient	9,596 (2,586, 16,606)	N/A	N/A	N/A
Overdose-specific ER	1,395 (1,069, 1,722)	N/A	N/A	N/A
Overdose-specific outpatient	82 (-1, 165)	N/A	N/A	N/A
Overdose-specific others	32 (0, 64)	N/A	N/A	N/A

Results

<u>Specific Aim 2B: Incremental Cost and Resource Utilization in Family Members of Prescription Opioid User and Others</u>

The results of the propensity score matching are reported followed by the incremental resource utilization and cost estimates between non-users who suffered from an overdose event and those who did not.

<u>Propensity score matching diagnostics –</u>

The distribution of the computed propensity scores before and after matching are shown in Figure 17 and 18 respectively.

The K-S statistic before matching was 4.08, p-value<0.0001 and after matching was 1.22, p-value = 0.1037. This indicates that the propensity scores have similar distributions across the patients who suffered from and overdose and those who did not after matching.

The baseline characteristics before and after matching for non-medical users are presented in Table 40 and Table 41 respectively. The mean propensity scores before and after matching are also presented.
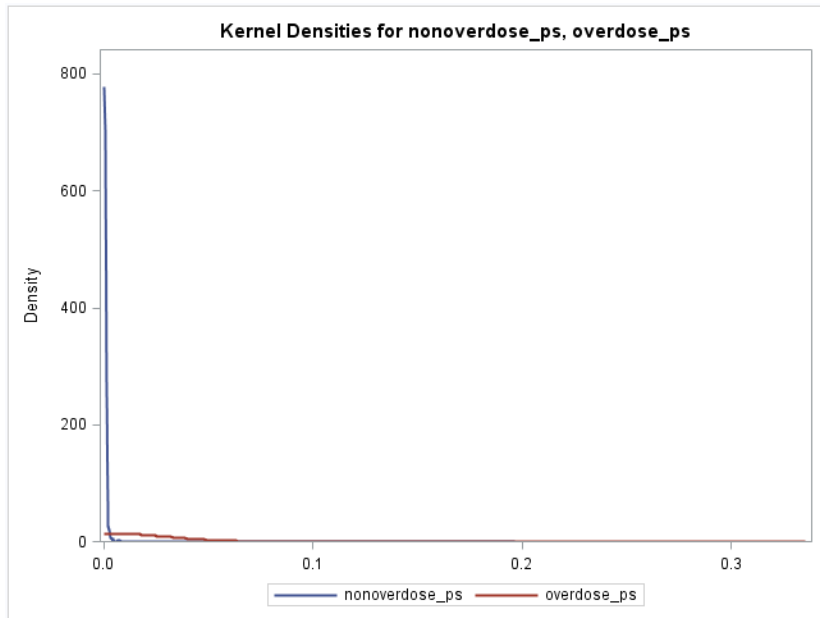
Figure 17 – Propensity score distributions before matching
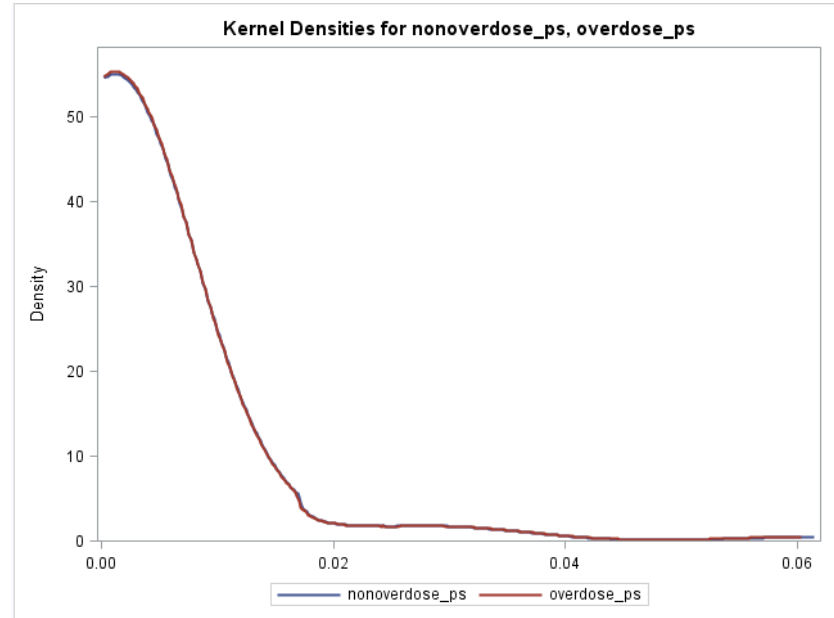
Figure 18 – Propensity score distributions after matching

Table 40 – Baseline characteristics for non-medical users before matching

Characteristics	Overdose cohort (N = 123)	Control cohort (N = 201,354)	ASD
Age group (years)			
0-17	19 (15.45)	99,376 (49.35)	0.777
18-44	60 (48.78)	63,699 (31.64)	0.355
45-64	33 (26.83)	31,863 (15.82)	0.271
65 and above	11 (8.94)	6,416 (3.19)	0.243
Sex, n (%)			
Female	70 (56.91)	97,553 (48.45)	0.17
Male	53 (43.09)	103,801 (51.55)	0.17
CCI Score, mean (SD)	0.23 (0.86)	0.07 (0.33)	0.246
Other comorbidities, n (%)			
Alcohol abuse	1 (0.81)	211 (0.10)	0.106
Drug abuse	10 (8.13)	588 (0.29)	0.398
Psychoses	3 (2.44)	314 (0.16)	0.202
Depression	18 (14.63)	4,985 (2.48)	0.445
Baseline healthcare costs, mean (SD)	13,101 (62,071)	2,128 (19,014)	0.239
Propensity score, mean (SD)*	0.006 (0.03)	0.0006 (0.002)	

ASD = Absolute Standardized Differences; CCI = Charlson Comorbidity Index; SD = Standard Deviation
 *This variable was not included in the model

Table 41 – Baseline characteristics for non-medical users after matching

Characteristics	Overdose cohort (N = 122)	Control cohort (N = 122)	ASD
Age group (years)			
0-17	19 (15.57)	30 (24.59)	0.227
18-44	59 (48.36)	54 (44.26)	0.082
45-64	33 (27.05)	29 (23.77)	0.075
65 and above	11 (9.02)	9 (7.38)	0.06
Sex, n (%)			
Female	69 (56.56)	58 (47.54)	0.181
Male	53 (43.44)	64 (52.46)	0.181
CCI Score, mean (SD)	0.23 (0.86)	0.35 (0.64)	0.158
Other comorbidities, n (%)			
Alcohol abuse	1 (0.82)	8 (6.56)	0.308
Drug abuse	9 (7.38)	8 (6.56)	0.032
Psychoses	2 (1.64)	5 (4.10)	0.148
Depression	17 (18.03)	22 (13.93)	0.112
Baseline healthcare costs, mean (SD)	7,946 (24,280)	29,561 (74,021)	0.392
Propensity score, mean (SD)*	0.003 (0.008)	0.003 (0.008)	

ASD = Absolute Standardized Difference; CCI = Charlson Comorbidity Index; SD = Standard Deviation
*This variable was not included in the model

The propensity score matching process was not able to balance the variables to the requirement in this study (ASD <0.1) (Table 41). To account for this imbalance between the two groups regression analysis was performed and age, sex, CCI score, alcohol abuse, psychoses, depression and log of baseline healthcare costs were included in the model to obtain adjusted incremental costs and resource utilization. We transformed the baseline healthcare cost variable to its logarithmic form so as to meet the assumptions of linear regression.

The proportion of patients who had a medical encounter is categorized by place of service and presented in Table 42. Unadjusted estimates for healthcare utilization by place of service for non-medical users are presented in Table 43.

Table 42 – Unadjusted healthcare resource utilization for non-medical users with and without at least one overdose event in the follow-up period in a matched population (Number of patients)

Variable	Cases	Control	p-value
Patients, n	122	122	
Resource utilization, n (%)			
All-cause inpatient visits	78 (63.93)	14 (11.48)	<0.0001
All-cause ER visits	107 (87.70)	24 (19.67)	<0.0001
All-cause outpatient visits	115 (94.26)	106 (86.89)	0.0486
All-cause other visits	92 (75.41)	64 (52.46)	0.0002
Overdose-specific inpatient *	55 (45.08)	N/A	N/A
Overdose-specific ER visits*	82 (67.21)	N/A	N/A
Overdose-specific outpatient visits*	10 (8.20)	N/A	N/A
Overdose-specific other visits*	2 (1.64)	N/A	N/A

*Are not mutually exclusive

Table 43 – Unadjusted healthcare resource utilization for non-medical users with and without at least one overdose event in the follow-up period in a matched population (Number of visits)

Resource utilization, Mean (SD)	Cases	Controls	Difference	p-value
Patients, n	122	122		
All-cause inpatient visits	1.58 (3.34)	0.29 (1.42)	1.30 (3.62)	<0.0001
All-cause ER visits	2.97 (5.17)	0.60 (1.93)	2.37 (5.48)	<0.0001
All-cause outpatient visits	15.22 (17.71)	8.76 (11.92)	6.50 (20.70)	0.0008

All-cause other visits	6.19 (12.26)	6.01 (12.26)	0.18 (32.05)	0.9506
Overdose-specific inpatient	0.47 (0.53)	N/A	N/A	N/A
Overdose-specific ER visits	0.85 (0.84)	N/A	N/A	N/A
Overdose-specific outpatient visits	0.23 (1.07)	N/A	N/A	N/A
Overdose-specific other visits	0.02 (0.13)	N/A	N/A	N/A

Unadjusted healthcare costs for non-users by place of service are presented in Table 44.

Table 44 – Unadjusted healthcare costs for non-medical users with and without at least one overdose event in the follow-up period in a matched population

Mean health care cost, US$ (95% CI)	Cases (N=122)	Controls (N=122)	Cost difference	p-value
All-cause health care costs	40,104 (25,296, 54,911)	17,387 (2,182, 32,591)	22,717 (1,920, 43,514)	0.0325
All-cause inpatient	22,256 (11,400, 33,112)	3,728 (-892, 33,112)	18,528 (6,599, 30,458)	0.0026
All-cause ER	4,049 (1,566, 6,532)	448 (225, 670)	3,601 (1,104, 6,099)	0.0051
All-cause outpatient	5,885 (2,410, 9,360)	3,682 (1,877, 5,487)	2,203 (-1,390, 5,796)	0.2272
All-cause others	7,059 (1,806, 12,312)	6,590 (-3,186, 16,365)	469 (-10,685, 11,623)	0.9338
Pharmacy costs	855 (496, 1,213)	2,940 (496, 5,384)	-2085 (-4,572, 402)	0.0996
Overdose-specific inpatient	9,963 (45,577)	N/A	N/A	N/A
Overdose-specific ER	923 (1,824)	N/A	N/A	N/A
Overdose-specific outpatient	163 (1,725)	N/A	N/A	N/A
Overdose-specific others	24 (199)	N/A	N/A	N/A

Incremental resource utilization

Healthcare resource utilization was different for every category of place of service between the cases and the control groups during the follow-up period (Table 45). This indicates that including the overdose event, the cases had greater healthcare resource utilization as compared to the controls. (All p-values <0.05).

Table 45 – Adjusted healthcare resource utilization for non-medical users with and without at least one overdose event in the follow-up period in a matched population

Resource utilization, Mean (95% CI)	Cases	Controls	Adjusted difference in resource utilization (95% CI)	p-value
Patients, n	122	122		
All-cause inpatient visits	1.57 (1.26, 1.88)	0.38 (0.14, 0.62)	1.19 (0.79, 1.59)	<0.0001
All-cause ER visits	3.20 (2.75, 3.64)	0.52 (0.29, 0.75)	2.68 (2.18, 3.18)	<0.0001
All-cause outpatient visits	15.11 (14.40, 15.82)	8.83 (8.29, 9.37)	6.28 (5.37, 7.20)	<0.0001
All-cause other visits	10.05 (8.40, 11.71)	4.10 (3.18, 5.03)	5.95 (4.23, 7.60)	<0.0001
Overdose-specific inpatient visits	0.47 (0.37, 0.56)	N/A	N/A	N/A
Overdose-specific ER visits	0.85 (0.70, 1.00)	N/A	N/A	N/A
Overdose-specific outpatient visits	0.23 (0.04, 0.42)	N/A	N/A	N/A
Overdose-specific other visits	0.02 (-0.006, 0.04)	N/A	N/A	N/A

<u>Incremental cost</u>

The incremental difference between all cause healthcare cost for non-medical users who suffered from an overdose and those who did not was estimated to be $41,102 (P-value <0.05) (Table 46). The cost difference for all-cause ER and all-cause outpatient services were found to be significantly different between the two groups. Overdose-specific healthcare costs were estimated to be $11,070. The Stata outputs for incremental cost and resource utilization estimation are presented in Appendix B. The effect size of the incremental all-cause healthcare costs was estimated to be 0.81. According to Cohen's interpretation of effect size, an effect size greater than 0.8 represents a large effect size.

Table 46 – Adjusted healthcare costs for non-medical users with and without at least one overdose event in the follow-up period in a matched population

Mean health care cost, US$ (95% CI)	Cases (N=122)	Controls (N=122)	Cost difference (95% CI)	p-value
All-cause health care costs	53,626 (26,878, 80,374)	12,524 (6,142, 18,905)	41,102 (15,052, 67,153)	0.002
All-cause inpatient	23,773 (10,013, 37,533)	6,135 (-4,860, 17,129)	17,638 (1,511, 37,353)	0.032
All-cause ER	3,741 (2,518, 4,964)	463 (119, 806)	3,279 (2,518, 4,964)	<0.0001
All-cause outpatient	6,191 (3,467, 8,915)	3,192 (1,784, 4,601)	2,999 (77, 5921)	0.044
All-cause others	14,363 (2,551, 26,174)	2,204 (709, 3,698)	12,159 (718, 23,598)	0.037
Pharmacy costs	1,687 (641, 2732)	1,886 (1028, 2744)	-199 (-1,290, 892)	0.721
Overdose-specific inpatient	9,963 (1,793, 18,132)	N/A	N/A	N/A
Overdose-specific ER	923 (596, 1,250)	N/A	N/A	N/A
Overdose-specific outpatient	163 (-146, 472)	N/A	N/A	N/A
Overdose-specific others	24 (-11, 60)	N/A	N/A	N/A

Table 47 and Table 48 list the five diagnoses with the highest per patient cost for patients who suffered from an overdose and patients who did not respectively. When compared to prescription opioid users who suffered from an overdose, the non-medical user overdose group does not have any diagnoses that indicate signs of abuse.

Table 47 – Diagnoses with the highest costs in the follow-up year for non-user who suffered from an overdose

Diagnosis Description	ICD-9 CM Code	Cost per patient ($)
1. Chronic osteomyelitis involving ankle	730.17	170,945
2. Other diseases of esophagus	530.89	141,815
3. End stage renal disease	304.00	93,685
4. Methicillin resistant staphylococcus aureus	041.12	87,732
5. Other mechanical complication of other internal orthopedic device, implant and graft	996.49	61,625

Table 48 – Diagnoses with the highest costs in the follow-up year for non-medical users who did not suffer from an overdose

Diagnosis Description	ICD-9 CM Code	Cost per patient ($)
1. Edward's Syndrome	758.2	595,290
2. Acute and chronic respiratory failure	518.84	75,421
3. Eating disorder, unspecified	307.50	69,822
4. Bacteremia	790.7	51,315
5. Fitting and adjustment of automatic implantable cardiac defibrillator	V53.32	50,449

Table 49 and Table 50 list the most commonly occurring diagnoses for patients who suffered from an overdose and those who did not respectively. In patients who suffered from an overdose, two out of five are codes for depression and one is for pain.

Table 49 – Most frequent diagnoses in the follow-up year for non-medical users who suffered from an overdose, excluding overdose diagnoses

Diagnosis Description	ICD-9 CM Code	Number of patients
1. Poisoning by unspecified drug or medicinal substances	977.9	45
2. Major depressive affective disorder, recurrent episode, unspecified	296.30	30
3. Depressive disorder, not elsewhere classified	311	29
4. Alteration of consciousness, other	780.09	24
5. Abdominal pain, unspecified site	789.00	20

Table 50 – Most frequent diagnoses in the follow-up year for non- medical users who did not suffer from an overdose

Diagnosis Description	ICD-9 CM Code	Number of patients
1. Need for prophylactic vaccination and inoculation against other specified disease	V05.8	47
2. Routine infant or child health check	V20.2	24
3. Acute upper respiratory infections of unspecified site	465.9	16
4. Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled	250.00	14
5. Major depressive affective disorder, recurrent episode, severe, specified as with psychotic behavior	296.34	11

<div align="center">**Sensitivity Analyses**</div>

1. Exclude patients with costs in the follow-up year greater than 1 million

None of the patients in the non- medical user group had costs in the follow-up period greater than $1 million and therefore, we did not carry

out this sensitivity analysis for this cohort.

2. Exclude patients with ESRD

In the non-medical user group, six patients (all cases) had claims for ESRD in the follow-up period. We assessed for balance after excluding

the six patients – balance was not achieved for age, sex, CCI score, baseline cost and psychosis. GLM was used to obtain adjusted estimates.

The results are presented in Table 51.

Table 51 – Sensitivity Analysis – Adjusted healthcare costs for non-medical users with and without at least one overdose event in the follow-up period in a matched population after excluding patients with ESRD

Mean health care cost, US$ (95% CI)	Cases (N=116)	Controls (N=122)	Cost difference (95% CI)	p-value
All-cause health care costs	54,077 (23,069, 85,085)	10,866 (5,841, 15,891)	43,211 (12,780, 73,642)	0.005
All-cause inpatient	20,412 (7,459, 33,365)	4,681 (13,783)	15,732 (-1,398, 32,861)	0.072
All-cause ER	3,811 (2,523, 5,099)	408 (91, 724)	3,403 (2,085, 4,722)	<0.0001
All-cause outpatient	6,693 (3,494, 9,893)	2,940 (1,658, 4,221)	3,754 (391, 7,117)	0.029
All-cause others	13,102 (959, 25,246)	1,939 (606, 3,273)	11,163 (-404, 22,729)	0.059
Pharmacy costs	2,061 (394, 3,728)	1,684 (830, 2,537)	377 (-1,106, 1,861)	0.50
Overdose-specific inpatient	9,013 (596, 17,431)	N/A	N/A	N/A
Overdose-specific ER	965 (623, 1308)	N/A	N/A	N/A
Overdose-specific outpatient	172 (-154, 497)	N/A	N/A	N/A
Overdose-specific others	26 (-12, 63)	N/A	N/A	N/A

3. Adopted 6-month baseline and 6-month follow-up

We obtained a sample of 150 cases and 219,760 controls after assessing for eligibility and obtained 149 matched pairs after propensity score matching. We assessed for balance after excluding the six patients – balance was not achieved for CCI score, baseline cost and depression. GLM was used to obtain adjusted estimates. The results of this analysis are presented in Table 52.

Table 52 – Sensitivity Analysis – Adjusted healthcare costs for non-medical users with and without at least one overdose event in a 6 month follow-up period in a matched population

Mean health care cost, US$ (95% CI)	Cases (N=149)	Controls (N=149)	Cost difference (95% CI)	p-value
All-cause health care costs	33,429 (19,931, 46,568)	8,756 (5,440, 12,073)	24,493 (10,777, 38,210)	<0.0001
All-cause inpatient	14,702 (7,627, 21,777)	3,212 (-580, 7,003)	11,490 (3,444, 19,536)	0.005
All-cause ER	2,834 (1,971, 3,697)	175 (17, 334)	2,659 (1,780, 3,538)	<0.0001
All-cause outpatient	7,240 (2,105, 12,375)	3,512 (814, 6,209)	3,728 (-2,006, 9,462)	0.203
All-cause others	4,309 (400, 8,219)	589 (516, 2,827)	2,638 (-1,600, 6,875)	0.222
Pharmacy costs	514 (265, 764)	579 (342, 817)	-65 (-388, 258)	0.693
Overdose-specific inpatient	8,023 (1,414, 14,631)	N/A	N/A	N/A
Overdose-specific ER	1,031 (675, 1,387)	N/A	N/A	N/A
Overdose-specific outpatient	130 (-123, 383)	N/A	N/A	N/A
Overdose-specific others	23 (-9, 55)	N/A	N/A	N/A

Cost Curve

The costs on the day of the overdose (time point 0) and subsequently after the overdose in prescription opioid users are shown in Figure 19.
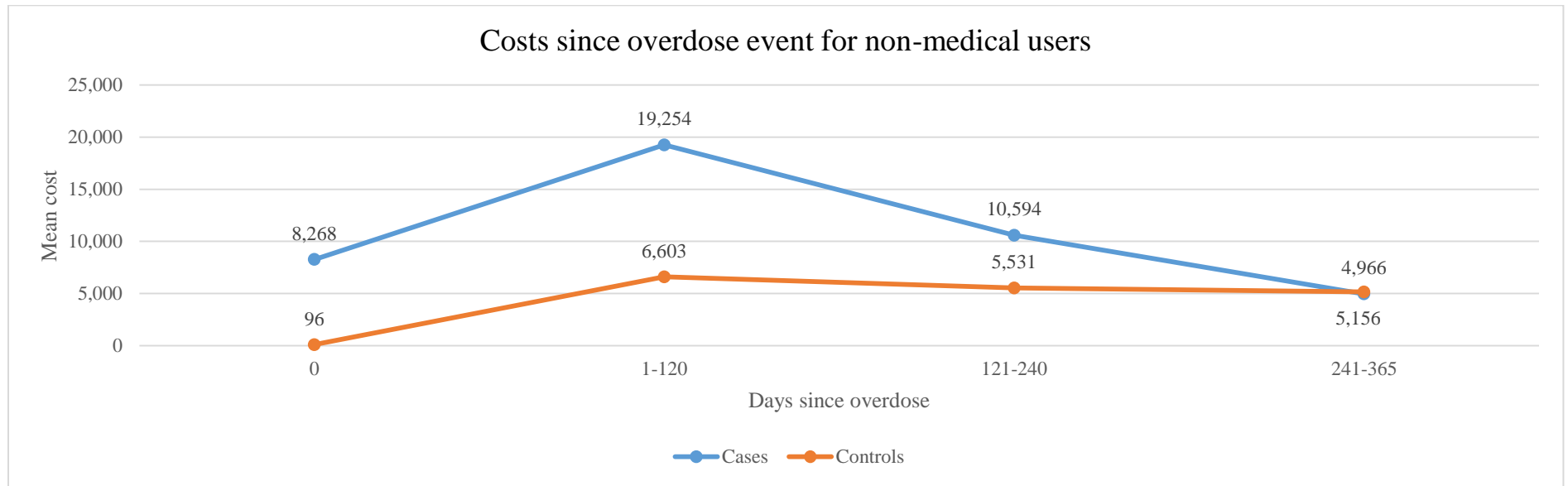
Figure 19 - Costs since overdose event for non-medical users (unadjusted)

CHAPTER V:

Discussion

<u>Aim 1</u>

The sample for our analysis was commercially enrolled beneficiaries in SelectHealth plans who were prescribed an opioid, their families and patients who suffered from a prescription opioid overdose. The majority of the sample was less than 65 years (94.11%) and female (53%).

The prevalence of prescription opioid overdoses in the study population was estimated to be 16.83 in 2011 and 36.9 per 100,000 in 2014, showing an increase of 119.2% over three years. We captured overdoses that were presented as Emergency Room (ER) visits, inpatient visits, outpatient visits or in other settings. To the best of our knowledge, there have not been any studies that have published opioid overdose prevalence rates for the same time period, but national rate of opioid overdoses tripled from 2000-2014. [2]

Two studies have published national prevalence rates of opioid poisoning close to the time frame of our study. Inocencio et al. reported prevalence for ED visits only and Fulton-Kehoe et al. reported prevalence for inpatient visits only.

Inocencio et al. estimated the prevalence of ER visits for prescription opioid overdoses for 2009 using DAWN data and reported a prevalence of 130.5 per 100,000.[4] DAWN was a public health surveillance system that monitored drug-related ER visits across the United States. These estimates were obtained using surveillance data as compared to administrative data, which could explain why this estimate is not comparable to ours.

Fulton-Kehoe et al. estimated the prevalence of inpatient visits for prescription opioid overdoses from 2004-2010 using National Inpatient Sample (NIS) and reported a prevalence of 12.6 per 100,000 in 2010 and a change in prevalence of 366.70% from 2004-2010. [69] The prevalence of prescription opioid overdoses in our sample was 16.83 per 100,000 in 2011. This is higher than the national sample, but can be attributed to our study capturing overdoses in all settings as compared to inpatient visits only.

We also reported the prevalence of opioid overdoses by group for prescription opioid users, family members of prescription opioid users and others (patients who did not have an identifiable source of opioid). The prevalence of opioid overdoses in prescription opioid users increased from 55.6 per 100,000 in 2011 to 102.77 per 100,000 in 2014 (84.83% increase). The prevalence of opioid overdoses in family members of prescription opioid users was 5.97 per 100,000 in 2011 and 8.23 per 100,000 in 2014, showing a 37.86% increase. The prevalence of overdoses in the other group increased by 180% from 2011 (8.24 per 100,000) to 2014 (23.07 per 100,000).

The Drug Abuse and Warning Network (DAWN) reported estimates of the change in the prevalence of ER visits attributable to the non-medical use of prescription opioids from 2004-2011 to be 183%. Non-medical use is defined by DAWN as taking a higher than prescribed or recommended dose of one's own medication, taking a pharmaceutical prescribed for another person, malicious poisoning of the patient by another individual, and documented substance

abuse involving pharmaceuticals. These estimates include opioid overdoses but may also include ER visits due to adverse reactions and hence, might not be comparable to our results. [112] While we estimated the change in prevalence of all opioid overdoses to be 119%, the non-medical use definition used by DAWN might be more appropriate for family members and others since these patients may be more likely to exhibit non-medical use behavior as compared to prescription users. We found an increase of 38% in overdoses for family members of prescription opioid users and 180% increase in the others group from 2011-2014. However, our study estimates are more recent, captured the prevalence specifically for overdose and were estimated for all settings as compared to only the ER.

The Centers for Disease Control and Prevention (CDC) published national estimates of age–adjusted death rates involving opioids (including heroin). They found that the mortality rate for opioids increased by 14% from 2013 (7.9 per 100,000) to 2014 (9 per 100,000). [2] While we did not have mortality data and could not compute death rates, we found that the prevalence of opioid overdoses increased by 16.67% from 2013 (31.63 per 100,000) to 2014 (36.9 per 100,000) in our study population.

Our study results showed hydrocodone and oxycodone were the most frequently prescribed opioids before an overdose. This finding is in line with national trends which state that hydrocodone and oxycodone are involved in most overdose deaths as compared to any other opioid. [2]

The average Morphine Equivalent Daily Dose (MEDD) in all prescription opioid users was 81.21 mg/day, while the MEDD in prescription opioid users who suffered from an overdose was 127.21 mg/day. Literature suggests 100 MEDD is the tipping point for increased risk of unintentional opioid overdose. The risk of an overdose increases by 9-fold for patients on doses ≥100 MEDD.[14,31,113]

The number of patients prescribed opioids chronically in our sample has steadily increased from 2011-2014 (Table 20). The prevalence of prescription opioid overdoses in acute users was 43.84 per 100,000 in 2011 and 50.28 per 100,000 in 2014 and that in chronic users was 187.03 per 100,000 in 2011 and 497.3 per 100,000 in 2014.

The prevalence of opioid overdoses in acute and chronic opioid users showed very different trends over the years (Figure 7). The prevalence in acute users showed a slight decrease in 2012 and 2013 as compared to 2011 and increased by 30% from 2013-2014. The prevalence of opioid overdoses in chronic users showed a sharp increase from 2011-2013 (166% increase) and was then steady from 2013 to 2014.

The increase in overdoses in chronic opioid users might have been due to increased opioid prescribing for chronic conditions. The steady rate of overdoses between 2013 and 2014 reflects changes that could have been brought about by the increasing awareness of the opioid epidemic. Data from 2015 is needed to be able to assess if this change is brought about by interventions aimed to reduce opioid overdoses or if it is coincidental. Since the prevalence of overdoses is much higher in chronic users as compared to acute users, interventions to reduce overdoses in patients who use opioids chronically are essential.

In March 2016, the CDC published guidelines for prescribing opioids for chronic pain. These guidelines explicitly state that opioids are not first line therapy for chronic pain. Clinicians are advised to use non-pharmacologic therapy and non-opioid pharmacologic therapy for chronic pain. If opioids are considered necessary, prescribers are advised evaluate risks for opioid related harms, use Prescription Drug Monitoring Programs (PDMPs), prescribe the lowest dose, prescribe immediate release opioids, and not prescribe more than 3 days' supply for acute pain.[94]

Aim 2

Incremental resource utilization – Prescription opioid-users

Resource utilization was significantly higher for all places of service in the follow-up year for users who suffered from an overdose as compared to those who did not (p<0.05) (Table 31). We expected users who have suffered from an overdose to have higher ER and inpatient use as a result of the overdose event but users who suffered from an overdose have higher resource utilization for outpatient visits and other services as well. Users who had an overdose had 1 more all-cause inpatient visit, 2 more all-cause ER visits, 6 more all-cause outpatient visits and 6 more all-cause other visits as compared to patients who did not have an overdose event.

When comparing all-cause inpatient and ER visits to overdose-specific inpatient and ER-visits for users who suffered from an overdose, we found that all-cause inpatient and ER visits were 277% and 294% higher than the overdose-specific inpatient and ER visits. This means that these patients had other inpatient and ER visits during the course of the follow-up year that are not related to the initial treatment of the overdose. The additional visits could be due to the users being more prone to using medical services, to having more than one overdose, or due to long-term effects of the overdose. However, since we have compared resource utilization between matched samples and there are patients who have more than one poisoning in the year, it is more likely that the increase in resource utilization is attributable to the long-term effects of opioid overdose. Long-term effects of opioid overdoses are discussed later in the discussion.

It is interesting to note that 13% of patients had a claim for an overdose in the outpatient setting and 4% had an overdose claim in other settings. The overdose claims classified as other visits were in the patient's home and ambulance. Other studies which have captured prevalence and

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costs due to overdose have captured ER visits and/or hospitalizations.[4,64,65,68–71] In this study, we

have also been able to capture prevalence and costs of opioid overdoses outside these settings.

Incremental resource utilization – Non-medical users

Resource utilization was significantly different for all places of service in the follow-up year for

non-medical users who suffered from an overdose as compared to non-medical users who did not

(Table 45). These findings are similar to the incremental resource utilization results for the user

group. Non- medical users who suffered from an overdose had 1 more inpatient visit, 2 more ER

visits, 6 more outpatient visits and 6 more other visits as compared to non-users who did not

suffer from an overdose (all p-values <0.05).

Similar to the prescription opioid user group, we found that average all-cause resource utilization

was 234% and 277% higher for ER and inpatient visits respectively as compared to overdose-

specific visits in this cohort of patients as well. Approximately 8% and 2% had overdose-specific

outpatient and other visits respectively.

Incremental costs – Prescription opioid users

The incremental all-cause health care costs for users who suffered from an overdose were

$65,277 (p-value<0.05) as compared to users who did not suffer from an overdose (Table 32).

All-cause inpatient costs account for nearly half of the incremental all-cause costs ($30,411).

Outpatient costs account for approximately one-fourth of the incremental all-cause costs

($15,329). Incremental all-cause ER costs were estimated to be $3,996. All-cause other and pharmacy incremental costs were $9,431 and $1,101 respectively (All p-values<0.05).

Incremental costs – Non-medical users

The incremental all-cause healthcare costs between non-medical users who suffered from an overdose and those who did not was estimated to be $41,102 (p<0.05) (Table 46). The incremental all-cause hospitalization and all-cause ER costs were estimated to be $17,638 and $3,279 respectively. The incremental all-cause other costs accounted for nearly 30% of the total all-cause incremental costs ($12,159). The incremental pharmacy costs were higher in non-users who did not suffer from an overdose by $199 and incremental all-cause outpatient costs were $2,999 (all p-values <0.05).

Overdose-specific costs

Two studies have estimated the ER and inpatient costs associated with an overdose. Hasegawa et al. reported the median ER and inpatient *charges* per patient for opioid overdoses over a year to be $4,521 and $22,460 respectively. [64] Yokell et al. estimated the mean ED and inpatient *charges* for all prescription opioid overdoses to be $3,640 and $29,497 respectively. [65] Inocencio et al. estimated the average cost per overdose to be $4,255 per poisoning event. [4]

We estimated the average overdose-specific costs per patient per year to be $12,111 for prescription opioid users and $11,070 for non-users. The average overdose-specific ER and inpatient costs for prescription opioid users were $1,498 (95%CI, 1,117-1,879) and $10,491

(95%CI, 1,450-19,532) respectively. The average overdose specific ER and inpatient costs for non-users were $923 (95%CI, 596- 1,250) and $9,963 (95%CI, 1,793-18,132).

Hasegawa et al. and Yokell et al. report higher estimates because they report charges and not costs. Charges between different hospitals can vary widely and are not a true reflection of the cost to the payer.[114] Based on estimates obtained from the Medical Expenditure Panel Survey (MEPS) data for ER and inpatient visits, charges were estimated to be nearly three times the costs.[115] Inocencio et al. applied a cost to charge ratio to the ER charge estimates in their study, but these ratios were from 2003 and this might have influenced the results. Also, ambulance costs were obtained from a 2006 GAO report and drug and device costs were obtained from the Red Book and an online emergency medical service company.[84–86] Therefore, inconsistency of data sources and the unavailability of recent data may have biased the results.

The incremental ER and inpatient costs were estimated to be $3,996 and $30,411 respectively for prescription opioid users and $3,279 and $17,638 respectively for non- medical users.

We examined the most frequent diagnoses in the follow-up year (excluding opioid overdoses) for the prescription opioid user cohort and for the non-medical user cohort to identify any lasting effects of the overdose. While we could not identify any specific effects looking at the five most frequent diagnoses, there are some common diagnosis themes that are seen in patients who suffered from an overdose in both groups. Patients in both groups suffered from depression which is a risk-factor for overdose and therefore, these patients are also likely to suffer from another overdose event. Poisoning by unspecified drugs was also seen in both groups and might represent another overdose event or it could also have been the opioid overdose event. There were instances when more than one overdose code was used for the same event. Alteration of consciousness could have been an additional code with the overdose since patients slip into

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unconsciousness after an overdose. Both groups had either one or more diagnoses for pain, which might have been the reason for taking the opioid medication. The diagnoses for pain were much more frequent in prescription opioid users, which is understandable because they were prescribed an opioid.

This analysis has shown that patients who suffered from an overdose, whether prescription opioid users on non-medical users, have a higher prevalence of certain risk factors (such as depression, non-opioid poisoning and pain) compared to individuals who did not. This suggests that these factors may have contributed to the higher per-patient costs of patients who suffered from an overdose as compared to the patients who did not.

While the relationship between opioid overdose and respiratory depression has been confirmed, the long-term effects on brain function are still being studied. Depressed respiration can affect the amount of oxygen that reaches the brain, a condition called hypoxia. Hypoxia can have short- and long-term psychological and neurological effects, including coma and permanent brain damage. [116] To our knowledge, only one study has looked at the long-term impact of overdose and it reported that overdoses can lead to cerebral hypoxia, pulmonary edema, pneumonia and cardiac arrhythmia. Overdoses may also lead to muscular impairment and neurological damage and the number of overdoses experienced is a significant predictor of poorer cognitive performance. [60] Costs due to these conditions may have been captured in the all-cause incremental costs for these patients and may have been the reason that all-cause costs and resource utilization were much higher than overdose-specific costs and resource utilization.

Strengths and Limitations

The analyses presented here highlight the substantial payer burden associated with patients who suffer from an opioid overdose. We are not aware of any other studies that have systematically quantified and compared the direct incremental costs of patients who suffered from an opioid overdose.

The availability of prescription and medical claims allowed us to identify a control group i.e., patients with an opioid prescription who did not suffer from a poisoning event. This allowed us to compare healthcare expenditures between the two groups after adjusting for comorbidities and other risk factors.

While other studies have estimated costs associated with opioid overdoses, they have not been able to account for prescription and patient characteristics in their studies due to data limitations.

Since we had family-level data we were able to estimate the prevalence and costs of opioid overdoses in family members of patients with an opioid prescription and patients who did not have a known and identifiable source for a prescription opioid. These estimates add to the literature on opioid diversion.

Our study has several limitations. Since the data is limited to Utah and Idaho, we did not have a nationally representative sample and hence, our estimates of prevalence and cost cannot be extrapolated to obtain national estimates. Utah ranked 4th and Idaho ranked 34th for all drug poisoning deaths in the United States from 2011-2014. [117]

Additionally, there are certain geographic differences between the states of Utah and the rest of the United States. For example, Utah has the nation's largest average household size at 3.14 as compared to an average household size of 2.63 in the United States.[118] Larger family sizes means that there are more members per household and hence, more people may have access to their family member's prescription opioids in Utah as compared to other states and this might be reflected in our estimates. The average household size in Idaho is 2.68, which is very similar to the national average.

We made the assumption that the source of the opioid in prescription opioid users and family members of prescription opioid users was the first opioid prescribed opioid to the prescription opioid user. We realize that this might not necessarily be accurate and that individuals from both these groups could have obtained opioids from other sources, but we do not have the means to verify this using claims data.

While we restricted the sample of recent prescription opioid users to patients for whom the time from when they were prescribed an opioid to the overdose was within one year, we did not apply the same time restriction to family members of prescription opioid users who suffered from an overdose. We made the assumption that the family members could use prescriptions that might have been around for longer than a year. In a sensitivity analysis, we tested this assumption by only including those family members for whom the time between the most recently prescribed opioid to a family member and overdose was one year. We found that 12 family members who suffered from an overdose did not meet the one year restriction and were moved to the others group.

We could not limit our study population to beneficiaries who were enrolled continuously over five years due to losing a large portion of our population – the sample of 667,718 enrollees

reduced to 74,226 enrollees. Not being able to restrict the sample to continuously enrolled patients affected various aspects of our study, as discussed below.

We identified patients as acute and chronic users for each year. We identified patients as chronic opioid users if the total days' supply for all the opioids that a patient was prescribed was greater than 120 days in that year. If a patient was prescribed an opioid in the last two months of the previous year and the first month of the current year, they were misclassified as an acute user in both years even though they were a chronic user across years. We could not use data across years to identify acute and chronic users because we did not have enrollment for patients across all years.

Another limitation of the study that stems from not having a large enough sample with continuous enrollment is that we had a baseline period of only 3 months. Not all comorbidities may have been documented during this period and this may have affected the performance of the propensity score match. We were able to capture comorbidities only if a patient had a medical encounter in the 3 months before the overdose. Some of the risk factors that we could have potentially captured better if we had a longer baseline period were mental illness (we accounted for depression and psychosis in this study), patients with a history of alcohol and substance abuse, and patients with a hospitalization 6 months before the overdose event and chronic opioid use.[36,37] If past medical history was available, some of the limitations of a short baseline period would have been accounted for. We carried out a sensitivity analysis and increased baseline period to 6 months to see how this affected our cost estimates. We found that the variables were better balanced in both the groups. The incremental cost over a six-month follow-up period was estimated to be $41,448 in prescription opioid users and $24,493 in non-medical users compared

to our original estimates for a twelve-month period of $65,277 in prescription opioid users and $41,102 in non-medical users.

Another limitation that follows from not being able to incorporate continuous enrollment over the five-year period is that the prevalence estimates might be underestimates of the true prevalence. The patients who have had an overdose may have had an overdose in the past or may have one in the future. However, if they were not enrolled in continuously through the study period we have not been able to capture it. Since we are not following the same population over five years, this might lead to underestimates or overestimates if we are not able to capture the true population denominator.

Other risk factors that we could not account for were demographic factors such as race, income and insurance type. While race might not be an important factor in this study since we used data from two fairly homogenous states, patients with low income and Medicaid patients are at a higher risk of suffering from an opioid overdose. [34] Being able to control for income and insurance type could have strengthened the propensity score model.

Even though we have matched cohorts of patients, propensity score methodology only controls for unobserved covariates if they are correlated with the observed covariates. One of the reasons that the difference in cost estimates between the cases and controls might not truly reflect downstream costs of opioid overdoses is that unobserved covariates are not accounted for. [119]

In case of misclassification or incorrect coding of opioid overdoses in claims data, cases and controls may not have been identified correctly (misclassification bias). While these databases are extremely rich sources of healthcare utilization data, they are generated to justify reimbursement and not for research purposes. Hence, these are coded to serve the purposes of

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reimbursement and may not always capture health care costs accurately.[120] For example, Inocencio et al. in their study found a higher prevalence of overdoses using DAWN (public health surveillance data) when compared to nationally representative administrative claims data. [4] With the implementation of the Affordable Care Act there are certain essential health benefits that are mandatory to be covered for all patients. Some of these health benefits that relate to opioid overdoses are emergency services, hospitalizations and services for substance abuse disorders and mental health. [121] This might have led to more accurate coding in recent years.

Additionally, while we have only included codes that capture prescription opioid overdoses (i.e. we did not include overdoses that were a result of heroin or an unidentified opioid). These overdoses may have been classified incorrectly and there is no way of knowing that the overdose occurred due to use of a specific prescription opioid, thereby biasing these estimates. However, this is a limitation that is inherent with claims data and these codes are used extensively in studies that examine overdoses using claims data.

Despite these limitations, this is the first study that used matched case-control methodology to estimate incremental resource utilization and costs as well as downstream costs for patients who suffer from an overdose due to a prescription opioid. Future studies should explore this area in a larger population and address limitations of our study.

Conclusion

In conclusion, our study found that the prevalence of opioid overdoses in chronic opioid users are much higher as compared to acute users. While the cost to payers due to overdoses in prescription opioid users is substantial, the diversion of prescription opioids has led to additional resource utilization and costs. We estimated the incremental cost per patient per year to be $65,277 in prescription opioid users who suffered from an overdose as compared to users who did not suffer from an overdose and $41,102 in non-medical users who suffered from an overdose as compared to non-users who did not. Resource utilization was significantly higher for all places of service in the follow-up year for prescription opioid users and non-users who suffered from an overdose as compared to their respective controls who did not suffer from an overdose. All-cause resource utilization was found to be higher than overdose-specific resource utilization for prescription opioid users ($65,277 vs. $12,111) as well as non-medical users (41,102 vs. $11,070). Additional research is needed to better understand the long-term impact of opioid overdose.

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Appendix A

Table A1 – ICD-9 CM Codes for Cancer

ICD-9-CM code	Description
140	Malignant neoplasm of lip
141	Malignant neoplasm of tongue
142	Malignant neoplasm of salivary glands
143	Malignant neoplasm of gum
144	Malignant neoplasm of floor of mouth
145	Malignant neoplasm of other parts of the mouth
146	Malignant neoplasm of oropharynx
147	Malignant neoplasm of nasopharynx
148	Malignant neoplasm of hypopharynx
149	Malignant neoplasm of other sites in the lip, oral cavity and pharynx
150	Malignant neoplasm of esophagus
151	Malignant neoplasm of stomach
152	Malignant neoplasm of small intestine including duodenum
153	Malignant neoplasm of colon
154	Malignant neoplasm of rectum rectosigmoid junction and anus
155	Malignant neoplasm of liver and intrahepatic bile ducts
156	Malignant neoplasm of gall bladder and extrahepatic bile ducts
157	Malignant neoplasm of pancreas
158	Malignant neoplasm of retroperitoneum and peritoneum
159	Malignant neoplasm of other sites within the digestive organs and peritoneum
160	Malignant neoplasm of nasal cavities, middle ear and accessory sinus
161	Malignant neoplasm of larynx
162	Malignant neoplasm of trachea, bronchus and lung
163	Malignant neoplasm of pleura
164	Malignant neoplasm of thymus, heart and mediastinum
165	Malignant neoplasm of other sites within the respiratory system and intrathoracic organs
170	Malignant neoplasm of bone and articular cartilage
171	Malignant neoplasm of connective tissue and other soft tissue
172	Malignant neoplasm of skin
173	Malignant neoplasm of other sites of the skin
174	Malignant neoplasm of female breast
175	Malignant neoplasm of male breast
176	Kaposi's sarcoma
179	Malignant neoplasm of utereus, part unspecified
180	Malignant neoplasm of cervix, uteri
181	Malignant neoplasm of placenta
182	Malignant neoplasm of body of uterus
183	Malignant neoplasm of ovary and other uterine adnexa
184	Malignant neoplasm of other and unspecified female genital organs

185	Malignant neoplasm of prostate
186	Malignant neoplasm of testis
187	Malignant neoplasm of penis and other male genital organs
188	Malignant neoplasm of bladder
189	Malignant neoplasm of kidney and other unspecified urinary organs
190	Malignant neoplasm of eye
191	Malignant neoplasm of brain
192	Malignant neoplasm of other and unspecified parts of the nervous system
193	Malignant neoplasm of thyroid gland
194	Malignant neoplasm of other endocrine glands and related structures
195	Malignant neoplasm of other and ill-defined sites
196	Secondary and unspecified malignant neoplasm of lymph nodes
197	Secondary malignant neoplasm of respiratory and digestive systems
198	Secondary malignant neoplasm of other specified sites
199	Malignant neoplasm without specification of site
200	Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue
201	Hodgkin's disease
202	Other malignant neoplasms of lymphoid and histiocytic tissue
203	Multiple myeloma and immunoproliferative neoplasms
204	Lymphoid leukemia
205	Myeloid leukemia
206	Monocytic leukemia
207	Other specified leukemia
208	Leukemia of unspecified cell type
209	Neuroendocrine tumors

Outputs for Incremental Resource Utilization and Incremental Cost Regression Models

Prescription Opioid Users – Incremental Resource Utilization

1. ER visits

```
Fitting probit regression for first part:

Iteration 0:   log likelihood = -263.22251
Iteration 1:   log likelihood = -176.10023
Iteration 2:   log likelihood = -174.94401
Iteration 3:   log likelihood = -174.93944
Iteration 4:   log likelihood = -174.93944

Fitting glm regression for second part:

Iteration 0:   log likelihood = -770.69936
Iteration 1:   log likelihood = -759.91976
Iteration 2:   log likelihood = -759.90358
Iteration 3:   log likelihood = -759.90358


Two-part model

-------------------------------------------------------------------------------

Log pseudolikelihood = -934.84302           Number of obs   =         396



Part 1: probit
-------------------------------------------------------------------------------
                                            Number of obs   =         396
                                            LR chi2(4)      =      176.57
                                            Prob > chi2     =      0.0000
Log likelihood = -174.93944                 Pseudo R2       =      0.3354

Part 2: glm
-------------------------------------------------------------------------------
```

```
                                                  Number of obs   =        245
Deviance        =  842.6044078                    (1/df) Deviance =  3.510852
Pearson         =  1594.509318                    (1/df) Pearson  =  6.643789

Variance function: V(u) = u                       [Poisson]
Link function    : g(u) = ln(u)                   [Log]

                                                  AIC             =  6.244111
Log likelihood   = -759.9035818                   BIC             = -477.6976
------------------------------------------------------------------------------
      sum_ed |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
probit       |
     overdose |
           1 |   1.902227    .162602    11.70   0.000     1.583533    2.220921
             |
    age_final |
           2 |   .3871682   .4004562     0.97   0.334    -.3977116    1.172048
           3 |   .1534738   .4001484     0.38   0.701    -.6308027    .9377504
           4 |   .2314768   .4516829     0.51   0.608    -.6538053    1.116759
             |
       _cons |  -.7365921   .3833504    -1.92   0.055    -1.487945    .0147608
-------------+----------------------------------------------------------------
glm          |
     overdose |
           1 |   .2986575   .0862591     3.46   0.001     .1295928    .4677222
             |
    age_final |
           2 |   .7999304   .3195979     2.50   0.012       .17353    1.426331
           3 |   .7148737    .321026     2.23   0.026     .0856743    1.344073
           4 |   .3683642   .3519755     1.05   0.295    -.3214951    1.058223
             |
       _cons |   .3021609   .3224269     0.94   0.349    -.3297842    .9341059
------------------------------------------------------------------------------
```

154

```
Average marginal effects                      Number of obs    =        396

Expression   : twopm combined expected values, predict()
dy/dx w.r.t. : 1.overdose


------------------------------------------------------------------------------
             |            Delta-method
             |     dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  1.overdose |  2.540564   .1897893    13.39   0.000     2.168584    2.912544
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.


Predictive margins                            Number of obs    =        396

Expression   : twopm combined expected values, predict()


------------------------------------------------------------------------------
             |            Delta-method
             |    Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |
           1 |  3.429131   .1488832    23.03   0.000     3.137325    3.720936
           2 |  .8885666   .1165933     7.62   0.000     .6600479    1.117085
------------------------------------------------------------------------------

.

end of do-file
```

155

2. Inpatient visits

```
Fitting probit regression for first part:



Iteration 0:   log likelihood = -269.61272
Iteration 1:   log likelihood = -208.17735
Iteration 2:   log likelihood = -207.74554
Iteration 3:   log likelihood = -207.74307
Iteration 4:   log likelihood = -207.74307


Fitting glm regression for second part:

Iteration 0:   log likelihood = -339.97556
Iteration 1:   log likelihood = -337.51863
Iteration 2:   log likelihood = -337.51057
Iteration 3:   log likelihood = -337.51057


Two-part model

--------------------------------------------------------------------------
Log pseudolikelihood = -545.25364           Number of obs   =        396

Part 1: probit
--------------------------------------------------------------------------
                                            Number of obs   =        396
                                            LR chi2(4)      =     123.74
                                            Prob > chi2     =     0.0000
Log likelihood = -207.74307                 Pseudo R2       =     0.2295

Part 2: glm
--------------------------------------------------------------------------
                                            Number of obs   =        167
Deviance        =   263.5472348             (1/df) Deviance =   1.626835
Pearson         =   506.3669634             (1/df) Pearson  =   3.125722

Variance function: V(u) = u                 [Poisson]
Link function    : g(u) = ln(u)             [Log]

                                            AIC             =   4.101923
Log likelihood   = -337.5105727             BIC             =  -565.5678
```

```
------------------------------------------------------------------------------
sum_inpati~t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
probit       |
     overdose |
           1 |   1.502703    .1460241    10.29   0.000     1.216501    1.788905
             |
    age_final |
           2 |    .7408724    .5025287     1.47   0.140    -.2440657    1.725811
           3 |    .8786724     .504048     1.74   0.081    -.1092436    1.866588
           4 |   1.251627     .547635     2.29   0.022     .1782822    2.324972
             |
       _cons |  -1.834893    .4998827    -3.67   0.000    -2.814645    -.855141
-------------+----------------------------------------------------------------
glm          |
     overdose |
           1 |    .3739636    .1492062     2.51   0.012     .0815248    .6664024
             |
    age_final |
           2 |    .0919023     .506289     0.18   0.856    -.9004058    1.084211
           3 |    .1916932    .5067236     0.38   0.705    -.8014668    1.184853
           4 |    .4198935    .5245535     0.80   0.423    -.6082126        1.448
             |
       _cons |    .3191836    .5217878     0.61   0.541    -.7035017    1.341869
------------------------------------------------------------------------------


Average marginal effects                        Number of obs     =        396



Expression   : twopm combined expected values, predict()

dy/dx w.r.t. : 1.overdose



------------------------------------------------------------------------------
             |            Delta-method
             |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  1.overdose |   1.355833    .1322435    10.25   0.000      1.09664    1.615025
------------------------------------------------------------------------------
```

Note: dy/dx for factor levels is the discrete change from the base level.

Predictive margins   Number of obs   =   396

Expression   : twopm combined expected values, predict()

             | Delta-method
             | Margin   Std. Err.   z   P>|z| [95% Conf. Interval]
-------------+--
    overdose |
           1 | 1.620543   .1197501   13.53   0.000   1.385837   1.855249
           2 | .2647099   .0557083   4.75   0.000   .1555237   .3738961

.

end of do-file

3. Outpatient visits

```
Iteration 0:   log likelihood = -3303.6224
Iteration 1:   log likelihood = -3267.3872
Iteration 2:   log likelihood = -3267.2892
Iteration 3:   log likelihood = -3267.2892

Generalized linear models                     No. of obs      =        396
Optimization     : ML                         Residual df     =        391
                                              Scale parameter =          1
Deviance         =  4899.673625               (1/df) Deviance =   12.53113
Pearson          =  6351.898458               (1/df) Pearson  =   16.24526

Variance function: V(u) = u                   [Poisson]
Link function    : g(u) = ln(u)               [Log]

                                              AIC             =   16.52671
Log likelihood   = -3267.289247               BIC             =   2560.941


-------------------------------------------------------------------------
                |                 OIM
  sum_outpatient |    Coef.   Std. Err.      z    P>|z|    [95% Conf. Interval]
----------------+--------------------------------------------------------
     1.overdose |   .4121217   .0256854    16.04   0.000    .3617792    .4624642
                |
      age_final |
              2 |   .3442714   .0855326     4.03   0.000    .1766306    .5119122
              3 |   .4954678   .0853132     5.81   0.000    .3282571    .6626785
              4 |   .6252919   .0920336     6.79   0.000    .4449094    .8056744
                |
          _cons |   2.141166   .0835431    25.63   0.000    1.977425    2.304907
-------------------------------------------------------------------------
```

```
Average marginal effects                    Number of obs    =        396

Model VCE     : OIM


Expression    : Predicted mean sum_outpatient, predict()
dy/dx w.r.t. : 1.overdose


------------------------------------------------------------------------------
             |            Delta-method
             |     dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  1.overdose |  6.642965   .4118413    16.13   0.000     5.835771    7.450159
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.


.

. margins overdose,


Predictive margins                          Number of obs    =        396

Model VCE     : OIM


Expression    : Predicted mean sum_outpatient, predict()


------------------------------------------------------------------------------
             |            Delta-method
             |    Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |
          1  |  19.66792    .318623    61.73   0.000     19.04343    20.29241
          2  |  13.02496   .2569925    50.68   0.000     12.52126    13.52865
------------------------------------------------------------------------------
```

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4. Other visits

twopm sum_others ib2.overdose ib1.age_final, firstpart (probit) secondpart(glm, family(poisson) link (log))

Fitting probit regression for first part:

Iteration 0:   log likelihood = -215.84723
Iteration 1:   log likelihood = -188.27759
Iteration 2:   log likelihood = -188.0518
Iteration 3:   log likelihood = -188.05176
Iteration 4:   log likelihood = -188.05176

Fitting glm regression for second part:

Iteration 0:   log likelihood = -2630.4167
Iteration 1:   log likelihood = -2522.581
Iteration 2:   log likelihood = -2522.5343
Iteration 3:   log likelihood = -2522.5343

Two-part model

Log pseudolikelihood = -2710.586   Number of obs   =   396

Part 1: probit

                                               Number of obs   =   396
                                               LR chi2(4)   =   55.59
                                               Prob > chi2   =   0.0000
Log likelihood = -188.05176   Pseudo R2   =   0.1288

Part 2: glm

                                               Number of obs   =   303
Deviance   =   4057.558434   (1/df) Deviance =   13.61597
Pearson   =   8381.825642   (1/df) Pearson =   28.12693

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```
Variance function: V(u) = u                          [Poisson]
Link function   : g(u) = ln(u)                       [Log]

                                          AIC          =   16.68339
Log likelihood   = -2522.534259           BIC          =   2354.866
--------------------------------------------------------------------
  sum_others |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+------------------------------------------------------
probit       |
     overdose |
           1 |   .9405659   .1560945     6.03   0.000    .6346263    1.246505
             |
    age_final |
           2 |   .9258904   .3687404     2.51   0.012    .2031724    1.648608
           3 |   1.201343   .3715334     3.23   0.001    .4731509    1.929535
           4 |     1.6535   .4547588     3.64   0.000    .7621892    2.544811
             |
       _cons |  -.7160624   .3556843    -2.01   0.044   -1.413191    -.018934
-------------+------------------------------------------------------
glm          |
     overdose |
           1 |    .689651   .0436712    15.79   0.000     .604057    .7752449
             |
    age_final |
           2 |  -.0771242   .1892333    -0.41   0.684   -.4480147    .2937663
           3 |   .5957498   .1876744     3.17   0.002    .2279148    .9635849
           4 |   1.188143   .1913609     6.21   0.000    .8130822    1.563203
             |
       _cons |   1.290475   .1885568     6.84   0.000    .9209107     1.66004
--------------------------------------------------------------------


.

. margins, dydx(overdose)

Warning: cannot perform check for estimable functions.


Average marginal effects                    Number of obs     =       396
```

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```
Expression   : twopm combined expected values, predict()

dy/dx w.r.t. : 1.overdose


------------------------------------------------------------------------------
             |            Delta-method
             |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  1.overdose |    6.22668   .3822002    16.29   0.000      5.477581    6.975778
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.



.

. margins overdose,

Warning: cannot perform check for estimable functions.


Predictive margins                              Number of obs     =        396


Expression   : twopm combined expected values, predict()


------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     overdose |
           1 |   9.892069   .3141548    31.49   0.000      9.276337     10.5078
           2 |   3.665389   .2241005    16.36   0.000       3.22616    4.104618
------------------------------------------------------------------------------


end of do-file
```

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Prescription Opioid Users – Incremental Costs

1. All-cause costs

```
Iteration 0:   log likelihood = -4614.9511
Iteration 1:   log likelihood = -4529.3023
Iteration 2:   log likelihood = -4527.3992
Iteration 3:   log likelihood = -4527.3852
Iteration 4:   log likelihood = -4527.3852


Generalized linear models                    No. of obs      =        396

Optimization     : ML                        Residual df     =        391

                                             Scale parameter =   4.541037

Deviance         =   807.8319408             (1/df) Deviance =   2.066066

Pearson          =   1775.545341             (1/df) Pearson  =   4.541037


Variance function: V(u) = u^2                [Gamma]

Link function    : g(u) = ln(u)              [Log]


                                             AIC             =   22.89083

Log likelihood   = -4527.385175              BIC             =  -1530.901


------------------------------------------------------------------------------
             |                 OIM
    sum_cost |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  1.overdose |   1.638966    .2198071    7.46   0.000     1.208152     2.06978
             |
   age_final |
           2 |   1.573318     .572826    2.75   0.006        .4506    2.696037
           3 |    1.62512    .5771368    2.82   0.005     .4939526    2.756287
```

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```
         4 |    2.215431    .6680046      3.32   0.001      .9061659    3.524696
           |
      _cons |     8.02287     .570287     14.07   0.000      6.905128    9.140612
------------------------------------------------------------------------------

Average marginal effects                        Number of obs    =        396

Model VCE    : OIM


Expression   : Predicted mean sum_cost, predict()

dy/dx w.r.t. : 1.overdose



------------------------------------------------------------------------------
           |            Delta-method
           |     dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------+------------------------------------------------------------------
 1.overdose |  65277.12   13182.48      4.95   0.000     39439.94     91114.3
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.


Predictive margins                              Number of obs    =        396

Model VCE    : OIM


Expression   : Predicted mean sum_cost, predict()



------------------------------------------------------------------------------
           |            Delta-method
           |    Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------+------------------------------------------------------------------
  overdose |
         1 |  81007.14   12994.27      6.23   0.000     55538.85    106475.4
         2 |  15730.03    2397.38      6.56   0.000     11031.25     20428.8
------------------------------------------------------------------------------
```

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2. ER costs

Fitting probit regression for first part:

```
Iteration 0:   log likelihood =  -264.6264
Iteration 1:   log likelihood = -180.42481
Iteration 2:   log likelihood = -179.59547
Iteration 3:   log likelihood = -179.59371
Iteration 4:   log likelihood = -179.59371
```

Fitting glm regression for second part:

```
Iteration 0:   log likelihood = -2368.9882
Iteration 1:   log likelihood = -2346.7054
Iteration 2:   log likelihood = -2345.4705
Iteration 3:   log likelihood = -2345.4627
Iteration 4:   log likelihood = -2345.4627
```

Two-part model
```
-------------------------------------------------------------------------------
```
Log pseudolikelihood = -2525.0564   Number of obs   =   396

Part 1: probit
```
-------------------------------------------------------------------------------
```
                                               Number of obs   =   396

                                               LR chi2(4)   =   170.07

                                               Prob > chi2   =   0.0000

Log likelihood = -179.59371   Pseudo R2   =   0.3213

Part 2: glm

```
--------------------------------------------------------------------------------
                                              Number of obs    =        242
Deviance        =   337.4110422              (1/df) Deviance  =   1.423675
Pearson         =   470.9666919              (1/df) Pearson   =   1.987201

Variance function: V(u) = u^2                [Gamma]
Link function   : g(u) = ln(u)               [Log]

                                             AIC              =   19.42531
Log likelihood  =  -2345.46267               BIC              =  -963.4672
--------------------------------------------------------------------------------
      er_cost |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+-----------------------------------------------------------------
probit        |
      overdose |
            1 |   1.850771   .1586993    11.66   0.000     1.539726    2.161816
              |
     age_final |
            2 |   .3196991   .3981413     0.80   0.422    -.4606435    1.100042
            3 |   .1614674   .3980126     0.41   0.685     -.618623    .9415578
            4 |   .2344065   .4495105     0.52   0.602    -.6466179    1.115431
              |
         _cons |  -.7267969   .3813834    -1.91   0.057    -1.474295    .0207009
--------------+-----------------------------------------------------------------
glm           |
      overdose |
            1 |   .1324462   .2099557     0.63   0.528    -.2790594    .5439517
              |
     age_final |
            2 |   2.231618   .5897765     3.78   0.000     1.075677    3.387558
            3 |   2.181602    .593429     3.68   0.000     1.018502    3.344701
            4 |   2.045879   .6645902     3.08   0.002     .7433065    3.348452
              |
         _cons |   6.450095   .5934368    10.87   0.000      5.28698     7.61321
--------------------------------------------------------------------------------
```

```
Average marginal effects                          Number of obs      =        396


Expression    : twopm combined expected values, predict()

dy/dx w.r.t. : 1.overdose


------------------------------------------------------------------------------
             |            Delta-method
             |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  1.overdose |   3995.506   718.7325     5.56   0.000     2586.816    5404.195
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.




Predictive margins                                Number of obs      =        396


Expression    : twopm combined expected values, predict()


------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |
           1 |   5726.213    618.225     9.26   0.000     4514.514    6937.911
           2 |   1730.707   366.7221     4.72   0.000     1011.945    2449.469
------------------------------------------------------------------------------
```

3. Inpatient costs

```
Fitting probit regression for first part:



Iteration 0:   log likelihood = -269.29181
Iteration 1:   log likelihood = -208.81404
Iteration 2:   log likelihood = -208.38525
Iteration 3:   log likelihood = -208.38291
Iteration 4:   log likelihood = -208.38291


Fitting glm regression for second part:

Iteration 0:   log likelihood = -1972.8971
Iteration 1:   log likelihood = -1936.0155
Iteration 2:   log likelihood = -1935.9527
Iteration 3:   log likelihood = -1935.9526


Two-part model

-------------------------------------------------------------------------
Log pseudolikelihood = -2144.3356          Number of obs   =       396

Part 1: probit
-------------------------------------------------------------------------
                                           Number of obs   =       396
                                           LR chi2(4)      =    121.82
                                           Prob > chi2     =    0.0000
Log likelihood = -208.38291                Pseudo R2       =    0.2262


Part 2: glm

-------------------------------------------------------------------------
                                           Number of obs   =       166
Deviance        =   365.031372             (1/df) Deviance = 2.267276
Pearson         =   957.6491663            (1/df) Pearson  = 5.948131

Variance function: V(u) = u^2              [Gamma]
Link function    : g(u) = ln(u)            [Log]
```

```
                                                AIC              =   23.38497
Log likelihood   = -1935.952646                 BIC              =  -457.9987
------------------------------------------------------------------------------
 inpatient_~t |     Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
probit        |
     overdose |
            1 |   1.490906    .1459619    10.21   0.000     1.204826    1.776986
              |
    age_final |
            2 |   .7243258    .5015667     1.44   0.149    -.2587269    1.707378
            3 |   .8777545    .5030691     1.74   0.081    -.1082428    1.863752
            4 |     1.2481    .5466271     2.28   0.022     .1767306     2.31947
              |
        _cons |  -1.827711    .4988567    -3.66   0.000    -2.805452   -.8499701
--------------+---------------------------------------------------------------
glm           |
     overdose |
            1 |   .7474327    .5064159     1.48   0.140    -.2451243     1.73999
              |
    age_final |
            2 |   .6517187    1.748092     0.37   0.709    -2.774478    4.077916
            3 |   1.041935    1.752476     0.59   0.552    -2.392855    4.476725
            4 |   1.064627    1.851243     0.58   0.565    -2.563742    4.692996
              |
        _cons |   9.210802    1.797896     5.12   0.000     5.686991    12.73461
------------------------------------------------------------------------------



Average marginal effects                        Number of obs     =        396


Expression   : twopm combined expected values, predict()

dy/dx w.r.t. : 1.overdose
```

```
--------------------------------------------------------------------------
               |            Delta-method
               |    dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------+----------------------------------------------------------
  1.overdose   |  30411.01   8075.895     3.77   0.000     14582.55   46239.47
--------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.


Predictive margins                             Number of obs     =        396


Expression   : twopm combined expected values, predict()


--------------------------------------------------------------------------
               |            Delta-method
               |   Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------+----------------------------------------------------------
    overdose   |
           1   |  34335.89   7822.879     4.39   0.000     19003.33   49668.45
           2   |  3924.882   1825.448     2.15   0.032       347.07   7502.694
--------------------------------------------------------------------------


.

end of do-file
```

4. Outpatient costs

```
Iteration 0:   log likelihood = -4382.7346
Iteration 1:   log likelihood = -4097.9163
Iteration 2:   log likelihood = -4097.5232
Iteration 3:   log likelihood = -4097.5219
Iteration 4:   log likelihood = -4097.5219


Generalized linear models                     No. of obs      =        396
Optimization     : ML                         Residual df     =        391
                                              Scale parameter =   10.51825
Deviance         =  1099.108483               (1/df) Deviance =   2.811019
Pearson          =  4112.635131               (1/df) Pearson  =   10.51825


Variance function: V(u) = u^2                 [Gamma]

Link function    : g(u) = ln(u)               [Log]



                                              AIC             =   20.71981

Log likelihood   = -4097.521852               BIC             =  -1239.624



---------------------------------------------------------------------------
                |              OIM
outpatient_cost |    Coef.   Std. Err.      z    P>|z|    [95% Conf. Interval]
----------------+----------------------------------------------------------
     1.overdose |  1.169392   .354604     3.30   0.001    .4743811   1.864403
                |
      age_final |
              2 |  1.502715   .8713529    1.72   0.085   -.2051057   3.210535
              3 |  .7615865   .8866044    0.86   0.390   -.9761262   2.499299
              4 |  1.283735   1.02237     1.26   0.209   -.7200728   3.287543
                |
          _cons |  7.644392   .8771214    8.72   0.000    5.925266   9.363519
---------------------------------------------------------------------------
```

```
Average marginal effects                          Number of obs     =         396

Model VCE    : OIM


Expression   : Predicted mean outpatient_cost, predict()

dy/dx w.r.t. : 1.overdose



------------------------------------------------------------------------------
             |            Delta-method
             |     dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  1.overdose |  15329.32   5575.264     2.75   0.006     4402.007    26256.64
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.


.

. margins overdose,


Predictive margins                               Number of obs     =         396

Model VCE    : OIM


Expression   : Predicted mean outpatient_cost, predict()



------------------------------------------------------------------------------
             |            Delta-method
             |    Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |
          1  |  22234.31   5244.431     4.24   0.000     11955.42    32513.21
          2  |  6904.991   1798.902     3.84   0.000     3379.207    10430.77
------------------------------------------------------------------------------
```

5. Other costs

```
Fitting probit regression for first part:


Iteration 0:   log likelihood = -221.57936
Iteration 1:   log likelihood = -197.56251
Iteration 2:   log likelihood = -197.41542
Iteration 3:   log likelihood = -197.41541


Fitting glm regression for second part:

Iteration 0:   log likelihood = -3004.5281
Iteration 1:   log likelihood = -2865.0035
Iteration 2:   log likelihood = -2862.6974
Iteration 3:   log likelihood = -2862.6811
Iteration 4:   log likelihood = -2862.6811


Two-part model

-----------------------------------------------------------------------
Log pseudolikelihood = -3060.0965         Number of obs   =       396

Part 1: probit
-----------------------------------------------------------------------
                                          Number of obs   =       396
                                          LR chi2(4)      =     48.33
                                          Prob > chi2     =    0.0000
Log likelihood = -197.41541               Pseudo R2       =    0.1091

Part 2: glm
-----------------------------------------------------------------------
                                          Number of obs   =       298
Deviance        =  1055.539384            (1/df) Deviance = 3.602523
Pearson         =  3798.453619            (1/df) Pearson  = 12.96401

Variance function: V(u) = u^2            [Gamma]
Link function    : g(u) = ln(u)          [Log]

                                          AIC             = 19.24618
```

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```
Log likelihood   = -2862.681071                    BIC           = -613.709
-------------------------------------------------------------------------------
 others_cost |     Coef.    Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+-----------------------------------------------------------------
probit       |
    overdose |
           1 |   .8470326    .1511792    5.60   0.000     .5507268    1.143338
             |
   age_final |
           2 |   .8815926    .3662105    2.41   0.016     .1638332    1.599352
           3 |   1.174112    .3688836    3.18   0.001     .4511132     1.89711
           4 |   1.507522    .4430626    3.40   0.001      .639135    2.375908
             |
       _cons |  -.6877088    .3533679   -1.95   0.052    -1.380297    .0048796
-------------+-----------------------------------------------------------------
glm          |
    overdose |
           1 |    1.58492    .4329985    3.66   0.000     .7362582    2.433581
             |
   age_final |
           2 |   .1407963    1.647191    0.09   0.932     -3.08764    3.369232
           3 |   .5452201    1.648981    0.33   0.741    -2.686724    3.777164
           4 |   1.991364    1.768294    1.13   0.260    -1.474429    5.457158
             |
       _cons |   7.191259    1.664037    4.32   0.000     3.929805    10.45271
-------------------------------------------------------------------------------


Average marginal effects                        Number of obs    =        396


Expression   : twopm combined expected values, predict()

dy/dx w.r.t. : 1.overdose

-------------------------------------------------------------------------------
             |            Delta-method
             |     dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+-----------------------------------------------------------------
  1.overdose |  9430.524    3795.388    2.48   0.013       1991.7    16869.35
```

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```
--------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.




Predictive margins                          Number of obs    =         396


Expression   : twopm combined expected values, predict()



--------------------------------------------------------------------------
             |              Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+------------------------------------------------------------
    overdose |
           1 |   11166.38   3916.298     2.85   0.004     3490.581    18842.19
           2 |   1735.859    630.225     2.75   0.006      500.641    2971.078
--------------------------------------------------------------------------
```

6. Pharmacy costs

```
Iteration 0:   log likelihood = -3575.973
Iteration 1:   log likelihood = -3533.5122
Iteration 2:   log likelihood = -3533.1633
Iteration 3:   log likelihood = -3533.1631


Generalized linear models                      No. of obs       =        396
Optimization     : ML                          Residual df      =        391
                                               Scale parameter =    2.523649
Deviance       =   683.3335821                 (1/df) Deviance =    1.747656
Pearson        =   986.746564                  (1/df) Pearson  =    2.523649

Variance function: V(u) = u^2                  [Gamma]
Link function    : g(u) = ln(u)                [Log]

                                               AIC             =   17.86951
Log likelihood   = -3533.16309                 BIC             =  -1655.399

-----------------------------------------------------------------------------
             |                 OIM
   phar_cost |     Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+---------------------------------------------------------------
  1.overdose |   .3785697   .1600025     2.37   0.018     .0649705    .6921689
             |
   age_final |
          2  |   .8867081    .427394     2.07   0.038     .0490313    1.724385
          3  |   1.404489   .4291205     3.27   0.001      .563428     2.24555
          4  |   1.045968   .4934182     2.12   0.034     .0788861    2.01305
             |
       _cons |   6.650307   .4209417    15.80   0.000     5.825277    7.475338
-----------------------------------------------------------------------------


Average marginal effects                       Number of obs    =        396

Model VCE      : OIM
```

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```
Expression   : Predicted mean phar_cost, predict()

dy/dx w.r.t. : 1.overdose


------------------------------------------------------------------------------
             |            Delta-method
             |      dy/dx   Std. Err.       z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  1.overdose |   1101.021   480.2126     2.29   0.022     159.8213    2042.22
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.


Predictive margins                              Number of obs     =        396

Model VCE    : OIM


Expression   : Predicted mean phar_cost, predict()


------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.       z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |
           1 |   3493.532   404.1305     8.64   0.000     2701.45    4285.613
           2 |   2392.511   275.1801     8.69   0.000     1853.168   2931.854
------------------------------------------------------------------------------
```

<u>Non-users – Incremental resource utilization</u>

1. ER visits

```
Fitting probit regression for first part:


Iteration 0:   log likelihood = -168.46337
Iteration 1:   log likelihood = -97.524476
Iteration 2:   log likelihood = -96.366217
Iteration 3:   log likelihood = -96.365146
Iteration 4:   log likelihood = -96.365146

Fitting glm regression for second part:

Iteration 0:   log likelihood = -365.24234
Iteration 1:   log likelihood = -354.37719
Iteration 2:   log likelihood = -354.34622
Iteration 3:   log likelihood = -354.34622


Two-part model

-------------------------------------------------------------------------
Log pseudolikelihood = -450.71136            Number of obs   =        244

Part 1: probit
-------------------------------------------------------------------------
                                             Number of obs   =        244
                                             LR chi2(10)     =     144.20
                                             Prob > chi2     =     0.0000
Log likelihood = -96.365146                  Pseudo R2       =     0.4280

Part 2: glm
-------------------------------------------------------------------------
                                             Number of obs   =        131
Deviance        =   356.3116239             (1/df) Deviance =   2.969264
Pearson         =   439.5344177             (1/df) Pearson  =   3.662787

Variance function: V(u) = u                  [Poisson]
Link function    : g(u) = ln(u)              [Log]
```

```
                                            AIC          =  5.577805
Log likelihood   = -354.3462164             BIC          = -228.7121
------------------------------------------------------------------------
         sum_ed |     Coef.    Std. Err.      z     P>|z|    [95% Conf. Interval]
----------------+-------------------------------------------------------
probit          |
       overdose |
              1 |   2.269462    .2279632     9.96    0.000    1.822662    2.716261
                |
      age_final |
              2 |  -.7049595     .308816    -2.28    0.022   -1.310228   -.0996913
              3 |  -.5936604    .3262024    -1.82    0.069   -1.233005    .0456845
              4 |   .0230673    .4726306     0.05    0.961   -.9032716    .9494063
                |
         gender |
              2 |    .357899    .2222605     1.61    0.107   -.0777236    .7935216
                |
      cci_score |   -.046686     .129763    -0.36    0.719   -.3010169    .2076449
                |
      elx_grp_28 |
              1 |   .8398603    .5007042     1.68    0.093    -.141502    1.821222
                |
      elx_grp_30 |
              1 |   1.058552    .6357613     1.67    0.096   -.1875168    2.304622
                |
      elx_grp_31 |
              1 |  -.4585234    .2998457    -1.53    0.126    -1.04621    .1291634
                |
log_baseline_cost |  .003187    .0290198     0.11    0.913   -.0536909    .0600649
          _cons |  -.6803018    .3035904    -2.24    0.025   -1.275328   -.0852755
----------------+-------------------------------------------------------
glm             |
       overdose |
              1 |   .1815591    .1516583     1.20    0.231   -.1156858    .4788039
                |
      age_final |
              2 |   .1688993     .151763     1.11    0.266   -.1285507    .4663494
              3 |   .4613513    .1624143     2.84    0.005    .1430252    .7796774
              4 |   .0779566    .2163505     0.36    0.719   -.3460826    .5019958
                |
         gender |
```

```
            2  |   -.5529449    .1057043     -5.23   0.000     -.7601215    -.3457683
               |
      cci_score |   -.1546712    .0763988     -2.02   0.043     -.3044101    -.0049324
               |
      elx_grp_28 |
            1  |     .537184    .2423762      2.22   0.027      .0621354     1.012233
               |
      elx_grp_30 |
            1  |   -.0991649    .2703705     -0.37   0.714     -.6290814     .4307517
               |
      elx_grp_31 |
            1  |    .8016525    .1235299      6.49   0.000      .5595384     1.043767
               |
 log_baseline_cost |    .0843133    .0174543      4.83   0.000      .0501036      .118523
          _cons  |    .4631874    .2049811      2.26   0.024      .0614319      .864943
--------------------------------------------------------------------------------
```

Average marginal effects   Number of obs   =   244

Expression   : twopm combined expected values, predict()

dy/dx w.r.t. : 1.overdose


```
--------------------------------------------------------------------------------
             |            Delta-method
             |     dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+------------------------------------------------------------------
  1.overdose |   2.678185    .253755    10.55   0.000     2.180834    3.175536
--------------------------------------------------------------------------------
```
Note: dy/dx for factor levels is the discrete change from the base level.

Predictive margins   Number of obs   =   244

Expression   : twopm combined expected values, predict()

```
-----------------------------------------------------------------------
             |            Delta-method
             |    Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+---------------------------------------------------------
    overdose |
           1 |   3.196999   .2269984    14.08   0.000      2.75209    3.641908
           2 |   .5188136   .1180824     4.39   0.000     .2873765    .7502508
-----------------------------------------------------------------------


end of do-file
```

2. Inpatient visits

Fitting probit regression for first part:


```
Iteration 0:   log likelihood = -161.67466
Iteration 1:   log likelihood = -113.14335
Iteration 2:   log likelihood = -112.01492
Iteration 3:   log likelihood = -112.01365
Iteration 4:   log likelihood = -112.01365
```

Fitting glm regression for second part:

```
Iteration 0:   log likelihood =  -226.7823
Iteration 1:   log likelihood = -220.63213
Iteration 2:   log likelihood = -220.61283
Iteration 3:   log likelihood = -220.61283
```


Two-part model

```
------------------------------------------------------------------------
Log pseudolikelihood = -332.62648          Number of obs   =      244

Part 1: probit
------------------------------------------------------------------------
                                           Number of obs   =      244
                                           LR chi2(10)     =    99.32
                                           Prob > chi2     =   0.0000
Log likelihood = -112.01365                Pseudo R2       =   0.3072

Part 2: glm
------------------------------------------------------------------------
                                           Number of obs   =       92
Deviance       =  215.8543019             (1/df) Deviance =  2.664868
Pearson        =  337.1172029             (1/df) Pearson  =  4.161941

Variance function: V(u) = u               [Poisson]
Link function    : g(u) = ln(u)           [Log]

                                           AIC             =  5.035061
```

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```
Log likelihood   = -220.6128263                    BIC          = -150.4106
----------------------------------------------------------------------------
    sum_inpatient |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+---------------------------------------------------------
probit            |
         overdose |
                1 |   1.701103   .2150142     7.91   0.000     1.279683    2.122523
                  |
        age_final |
                2 |   .4907994   .2780572     1.77   0.078    -.0541827    1.035782
                3 |   .5479936   .2924207     1.87   0.061    -.0251404    1.121128
                4 |   .5186591   .3932459     1.32   0.187    -.2520888    1.289407
                  |
           gender |
                2 |   .0416975   .2052586     0.20   0.839     -.360602     .443997
                  |
        cci_score |   .1233415   .1579979     0.78   0.435    -.1863288    .4330117
                  |
        elx_grp_28 |
                1 |    .465346   .5140937     0.91   0.365    -.5422592    1.472951
                  |
        elx_grp_30 |
                1 |  -.2561456   .7010828    -0.37   0.715    -1.630243    1.117951
                  |
        elx_grp_31 |
                1 |   .0911531   .2766749     0.33   0.742    -.4511198    .6334259
                  |
  log_baseline_cost |    .088938   .0281786     3.16   0.002     .0337089     .144167
            _cons |  -2.308551   .3343774    -6.90   0.000    -2.963919   -1.653184
------------------+---------------------------------------------------------
glm               |
         overdose |
                1 |  -.1645824   .2236116    -0.74   0.462    -.6028531    .2736883
                  |
        age_final |
                2 |   .1963831   .2718678     0.72   0.470    -.3364679    .7292342
                3 |   .4108142   .2839624     1.45   0.148    -.1457419    .9673703
                4 |   .2448995   .2970152     0.82   0.410    -.3372396    .8270387
                  |
```

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```
      gender |
           2  |   -.5096374    .1407855    -3.62   0.000    -.7855719   -.2337028
              |
   cci_score  |    .0603846    .0644891     0.94   0.349    -.0660118     .186781
              |
   elx_grp_28 |
           1  |    -.750825    .5658585    -1.33   0.185    -1.859887    .3582373
              |
   elx_grp_30 |
           1  |    .0949317    .5039202     0.19   0.851    -.8927338    1.082597
              |
   elx_grp_31 |
           1  |    .3675877    .1708189     2.15   0.031     .0327888    .7023866
              |
log_baseline_cost |  .0763567    .0236478     3.23   0.001      .030008    .1227055
        _cons |    .4240338    .3073953     1.38   0.168    -.1784499    1.026517
------------------------------------------------------------------------------


Average marginal effects                        Number of obs     =        244


Expression   : twopm combined expected values, predict()

dy/dx w.r.t. : 1.overdose


------------------------------------------------------------------------------
             |            Delta-method
             |     dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  1.overdose |   1.187284   .2030539     5.85   0.000     .7893053    1.585262
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.


Predictive margins                              Number of obs     =        244


Expression   : twopm combined expected values, predict()
```

```
----------------------------------------------------------------------
             |            Delta-method
             |    Margin   Std. Err.      z    P>|z|    [95% Conf. Interval]
-------------+--------------------------------------------------------
    overdose |
           1 |   1.569207   .1580336    9.93   0.000    1.259467    1.878947
           2 |   .3819233   .1213076    3.15   0.002    .1441649    .6196818
----------------------------------------------------------------------


end of do-file
```

3. Outpatient visits

```
Iteration 0:   log likelihood =  -1941.436
Iteration 1:   log likelihood =  -1893.789
Iteration 2:   log likelihood = -1893.7576
Iteration 3:   log likelihood = -1893.7576
```

```
Generalized linear models                    No. of obs      =        244
Optimization     : ML                        Residual df     =        233
                                             Scale parameter =          1
Deviance         =  2927.152423              (1/df) Deviance =   12.56289
Pearson          =  4317.717983              (1/df) Pearson  =   18.53098

Variance function: V(u) = u                  [Poisson]
Link function    : g(u) = ln(u)              [Log]

                                             AIC             =   15.61277
Log likelihood   = -1893.757572              BIC             =   1646.312
```

```
--------------------------------------------------------------------------
               |                 OIM
sum_outpatient |    Coef.    Std. Err.      z     P>|z|    [95% Conf. Interval]
---------------+----------------------------------------------------------
    1.overdose |  .5375132    .0402109    13.37   0.000    .4587014    .6163251
               |
     age_final |
             2 |  .1369592    .0573686     2.39   0.017    .0245189    .2493995
             3 |  .3265451    .0581533     5.62   0.000    .2125668    .4405235
             4 | -.0006791     .082524    -0.01   0.993   -.1624232    .1610651
               |
      2.gender |  .0748006      .03978     1.88   0.060   -.0031669     .152768
     cci_score |   .030507    .0211669     1.44   0.150   -.0109793    .0719933
   1.elx_grp_28| -.7493537     .139098    -5.39   0.000   -1.021981   -.4767266
   1.elx_grp_30|  .4214614    .1028947     4.10   0.000    .2197914    .6231313
   1.elx_grp_31|  .0192083    .0510049     0.38   0.706   -.0807594     .119176
log_baseline_cost|  .082145    .0056316    14.59   0.000    .0711072    .0931828
         _cons |  1.456523    .0647182    22.51   0.000    1.329678    1.583369
--------------------------------------------------------------------------
```

```
Average marginal effects                          Number of obs     =          244
Model VCE    : OIM

Expression   : Predicted mean sum_outpatient, predict()
dy/dx w.r.t. : 1.overdose


--------------------------------------------------------------------------------
             |            Delta-method
             |     dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+------------------------------------------------------------------
  1.overdose |  6.282776   .4650145    13.51   0.000     5.371364    7.194188
--------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.



Predictive margins                                Number of obs     =          244
Model VCE    : OIM

Expression   : Predicted mean sum_outpatient, predict()


--------------------------------------------------------------------------------
             |            Delta-method
             |    Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+------------------------------------------------------------------
    overdose |
          1  |  15.11006   .3619223    41.75   0.000     14.40071    15.81942
          2  |  8.827287    .275168    32.08   0.000     8.287967    9.366606
--------------------------------------------------------------------------------

end of do-file
```

4. Other visits

Fitting probit regression for first part:

Iteration 0:   log likelihood = -159.52587
Iteration 1:   log likelihood = -134.23175
Iteration 2:   log likelihood = -133.89223
Iteration 3:   log likelihood = -133.89117
Iteration 4:   log likelihood = -133.89117

Fitting glm regression for second part:

Iteration 0:   log likelihood = -1383.0872
Iteration 1:   log likelihood = -1199.9319
Iteration 2:   log likelihood =   -1198.69
Iteration 3:   log likelihood = -1198.6893
Iteration 4:   log likelihood = -1198.6893

Two-part model

Log pseudolikelihood = -1332.5805   Number of obs   =   244

Part 1: probit

                                               Number of obs   =   244
                                               LR chi2(10)   =   51.27
                                               Prob > chi2   =   0.0000
Log likelihood = -133.89117   Pseudo R2   =   0.1607

Part 2: glm

                                               Number of obs   =   156

Deviance   =   1909.628994   (1/df) Deviance =   13.16986

Pearson   =   2749.959625   (1/df) Pearson =   18.96524

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```
Variance function: V(u) = u                        [Poisson]

Link function    : g(u) = ln(u)                     [Log]


                                          AIC          =  15.50884

Log likelihood   = -1198.689291           BIC          =     1177.4

-------------------------------------------------------------------------
     sum_others |     Coef.    Std. Err.      z    P>|z|    [95% Conf. Interval]
----------------+--------------------------------------------------------
probit          |
       overdose |
              1 |  .6784057   .1897298     3.58   0.000    .3065422    1.050269
                |
      age_final |
              2 |  .7965336   .2474413     3.22   0.001    .3115576     1.28151
              3 |  .5968794   .2625654     2.27   0.023    .0822607    1.111498
              4 |  .9150297   .4127336     2.22   0.027    .1060867    1.723973
                |
         gender |
              2 |  .4542447   .1895301     2.40   0.017    .0827725    .8257169
                |
      cci_score |  .2647693   .1966063     1.35   0.178   -.1205719    .6501106
                |
      elx_grp_28 |
              1 |   .936025   .6380629     1.47   0.142   -.3145553    2.186605
                |
      elx_grp_30 |
              1 | -.1069828   .5678184    -0.19   0.851   -1.219886    1.005921
                |
      elx_grp_31 |
              1 | -.2095275   .2534474    -0.83   0.408   -.7062753    .2872203
                |
log_baseline_cost |   .062733   .025224     2.49   0.013    .0132949    .1121711
          _cons | -1.162396   .2693916    -4.31   0.000   -1.690394   -.6343985
----------------+--------------------------------------------------------
glm             |
       overdose |
              1 |  .5562921    .070421     7.90   0.000    .4182695    .6943147
```

```
                    |
        age_final |
                2 |   -1.650641    .0896206    -18.42    0.000    -1.826294    -1.474988
                3 |   -.8932945    .0771312    -11.58    0.000    -1.044469    -.7421202
                4 |    -1.37713    .1105135    -12.46    0.000    -1.593732    -1.160527
                    |
          gender |
                2 |   -.0066167     .054279     -0.12    0.903    -.1130015     .0997681
                    |
       cci_score |    .1867462    .0214131      8.72    0.000     .1447774     .2287151
                    |
      elx_grp_28 |
                1 |   -1.068284    .2462421     -4.34    0.000     -1.55091    -.5856588
                    |
      elx_grp_30 |
                1 |    .1632291    .2387883      0.68    0.494    -.3047873     .6312456
                    |
      elx_grp_31 |
                1 |   -.3281661    .0946451     -3.47    0.001     -.513667    -.1426652
                    |
 log_baseline_cost |  .2301726    .0108194     21.27    0.000     .2089671     .2513782
           _cons |    1.015503    .1251469      8.11    0.000     .7702191     1.260786
-------------------------------------------------------------------------------


Average marginal effects                        Number of obs     =         244


Expression   : twopm combined expected values, predict()

dy/dx w.r.t. : 1.overdose


-------------------------------------------------------------------------------
            |             Delta-method
            |     dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+-----------------------------------------------------------------
  1.overdose |  5.946818    .8438828      7.05   0.000     4.292838     7.600797
-------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.
```

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```
Predictive margins                              Number of obs     =        244


Expression   : twopm combined expected values, predict()


------------------------------------------------------------------------------
             |            Delta-method
             |    Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     overdose |
           1 |   10.05121   .8442013    11.91   0.000      8.39661    11.70582
           2 |   4.104396   .4701557     8.73   0.000     3.182908    5.025885
------------------------------------------------------------------------------

.

end of do-file
```

Non-users – Incremental cost estimation

1. All-cause costs

```
Iteration 0:   log likelihood = -2659.7031
Iteration 1:   log likelihood = -2588.6215
Iteration 2:   log likelihood = -2575.6264
Iteration 3:   log likelihood = -2575.5877
Iteration 4:   log likelihood = -2575.5877

Generalized linear models                        No. of obs      =         244
Optimization     : ML                            Residual df     =         233
                                                 Scale parameter =    4.83807
Deviance         =   474.9786983                 (1/df) Deviance =   2.038535
Pearson          =   1127.270289                 (1/df) Pearson  =    4.83807

Variance function: V(u) = u^2                    [Gamma]
Link function    : g(u) = ln(u)                  [Log]

                                                 AIC             =    21.20154
Log likelihood   = -2575.587727                  BIC             =   -805.8615


---------------------------------------------------------------------------
             |                 OIM
    sum_cost |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+-------------------------------------------------------------
  1.overdose |   1.454419   .3198381     4.55   0.000     .8275482     2.08129
             |
   age_final |
           2 |   .1866414   .5082002     0.37   0.713    -.8094127    1.182696
           3 |    .750468   .5193165     1.45   0.148    -.2673736     1.76831
           4 |  -.0927814   .6397097    -0.15   0.885    -1.346589    1.161027
             |
    2.gender |  -.1475685   .3158639    -0.47   0.640    -.7666502    .4715133
   cci_score |  -.0463075   .2586336    -0.18   0.858      -.55322    .4606051
 1.elx_grp_28 |   -1.39919   .8119126    -1.72   0.085    -2.990509    .1921298
 1.elx_grp_30 |  -.2050553   .9159732    -0.22   0.823     -2.00033    1.590219
 1.elx_grp_31 |  -.8364814   .4150795    -2.02   0.044    -1.650022   -.0229407
```

```
log_baseline_cost |    .2709387    .0404346      6.70    0.000       .1916883     .3501891
            _cons |    7.306485     .5000464     14.61    0.000       6.326412     8.286558
--------------------------------------------------------------------------------


Average marginal effects                         Number of obs     =         244

Model VCE    : OIM


Expression   : Predicted mean sum_cost, predict()

dy/dx w.r.t. : 1.overdose


--------------------------------------------------------------------------------
             |             Delta-method
             |     dy/dx    Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+------------------------------------------------------------------
  1.overdose |   41102.28    13291.25     3.09    0.002     15051.9     67152.65
--------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.


Predictive margins                               Number of obs     =         244

Model VCE    : OIM


Expression   : Predicted mean sum_cost, predict()


--------------------------------------------------------------------------------
             |             Delta-method
             |    Margin    Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+------------------------------------------------------------------
    overdose |
           1 |   53625.84     13647.1     3.93    0.000     26878.01     80373.66
           2 |   12523.56    3255.912     3.85    0.000     6142.091     18905.03
--------------------------------------------------------------------------------
```

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2. ER costs

Fitting probit regression for first part:

```
Iteration 0:   log likelihood = -168.60295
Iteration 1:   log likelihood = -95.657801
Iteration 2:   log likelihood = -94.544993
Iteration 3:   log likelihood = -94.544025
Iteration 4:   log likelihood = -94.544025
```

Fitting glm regression for second part:

```
Iteration 0:   log likelihood = -1197.0403
Iteration 1:   log likelihood =  -1179.027
Iteration 2:   log likelihood = -1178.7198
Iteration 3:   log likelihood = -1178.7186
Iteration 4:   log likelihood = -1178.7186
```

Two-part model

```
-------------------------------------------------------------------------------

Log pseudolikelihood = -1273.2626           Number of obs   =        244

Part 1: probit
-------------------------------------------------------------------------------
                                            Number of obs   =        244
                                            LR chi2(10)     =     148.12
                                            Prob > chi2     =     0.0000
Log likelihood = -94.544025                 Pseudo R2       =     0.4393

Part 2: glm
-------------------------------------------------------------------------------
                                            Number of obs   =        130
Deviance         =   161.9366414            (1/df) Deviance = 1.360812
Pearson          =   212.4156339            (1/df) Pearson  = 1.785005

Variance function: V(u) = u^2              [Gamma]
```

```
Link function    : g(u) = ln(u)                         [Log]

                                              AIC              =   18.30336
Log likelihood  = -1178.718581               BIC              =    -417.3
------------------------------------------------------------------------------
        er_cost |     Coef.    Std. Err.      z     P>|z|    [95% Conf. Interval]
----------------+-------------------------------------------------------------
probit          |
       overdose |
              1 |   2.318329   .2307339    10.05   0.000    1.866098    2.770559
                |
      age_final |
              2 |  -.7411354   .3109235    -2.38   0.017   -1.350534   -.1317365
              3 |  -.5995424    .327574    -1.83   0.067   -1.241576    .042491
              4 |   .0360439   .4752967     0.08   0.940   -.8955206    .9676083
                |
         gender |
              2 |   .3202644   .2237752     1.43   0.152   -.1183268    .7588557
                |
      cci_score |  -.0455226   .1303803    -0.35   0.727   -.3010634    .2100182
                |
      elx_grp_28 |
              1 |   .8908504   .5025357     1.77   0.076   -.0941015    1.875802
                |
      elx_grp_30 |
              1 |   1.080977   .6382927     1.69   0.090   -.1700534    2.332008
                |
      elx_grp_31 |
              1 |  -.4437491   .3017793    -1.47   0.141   -1.035226    .1477274
                |
log_baseline_cost |  .0080193   .0292487     0.27   0.784   -.0493071    .0653456
          _cons |  -.7204174    .306217    -2.35   0.019   -1.320592   -.1202431
----------------+-------------------------------------------------------------
glm             |
       overdose |
              1 |   .3085878   .3788721     0.81   0.415   -.4339879    1.051164
                |
      age_final |
              2 |   .6598823   .3605457     1.83   0.067   -.0467742    1.366539
```

```
           3 |    .475668     .396337     1.20    0.230    -.3011381    1.252474
           4 |   .0303546    .4924477     0.06    0.951    -.9348252    .9955345
             |
      gender |
           2 |  -.5194774    .2657891    -1.95    0.051    -1.040414    .0014597
             |
   cci_score |  -.3722108    .1631738    -2.28    0.023    -.6920256   -.0523961
             |
  elx_grp_28 |
           1 |   .0440796    .7237874     0.06    0.951    -1.374518    1.462677
             |
  elx_grp_30 |
           1 |  -.1082225    .7302242    -0.15    0.882    -1.539436    1.322991
             |
  elx_grp_31 |
           1 |   .8343444     .425985     1.96    0.050    -.0005709     1.66926
             |
log_baseline_cost |   .0914062    .0365476     2.50    0.012     .0197742    .1630383
        _cons |   7.163403     .470287    15.23    0.000     6.241657    8.085148
------------------------------------------------------------------------------

Average marginal effects                        Number of obs     =        244



Expression    : twopm combined expected values, predict()

dy/dx w.r.t. : 1.overdose


------------------------------------------------------------------------------
             |            Delta-method
             |     dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  1.overdose |  3278.557    635.3301     5.16    0.000     2033.333    4523.781
------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.
```

```
Predictive margins                              Number of obs      =        244


Expression   : twopm combined expected values, predict()


------------------------------------------------------------------------------
             |            Delta-method
             |    Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     overdose |
           1 |   3741.048   624.0603     5.99   0.000     2517.913    4964.184
           2 |   462.4913   175.0305     2.64   0.008     119.4379    805.5447
------------------------------------------------------------------------------


.

end of do-file
```

3. Inpatient costs

```
Fitting probit regression for first part:



Iteration 0:   log likelihood = -160.63548
Iteration 1:   log likelihood = -107.90992
Iteration 2:   log likelihood = -106.32958
Iteration 3:   log likelihood = -106.32784
Iteration 4:   log likelihood = -106.32784


Fitting glm regression for second part:

Iteration 0:   log likelihood = -1028.7183
Iteration 1:   log likelihood = -1012.8525
Iteration 2:   log likelihood = -1012.3168
Iteration 3:   log likelihood = -1012.3111
Iteration 4:   log likelihood = -1012.3111


Two-part model

------------------------------------------------------------------------------
Log pseudolikelihood = -1118.6389           Number of obs   =        244

Part 1: probit
------------------------------------------------------------------------------
                                            Number of obs   =        244
                                            LR chi2(10)     =     108.62
                                            Prob > chi2     =     0.0000
Log likelihood = -106.32784                 Pseudo R2       =     0.3381

Part 2: glm
------------------------------------------------------------------------------
                                            Number of obs   =         90
Deviance         =  154.4116604             (1/df) Deviance = 1.954578
Pearson          =  238.1585207             (1/df) Pearson  = 3.014665

Variance function: V(u) = u^2               [Gamma]
Link function    : g(u) = ln(u)             [Log]
```

```
                                              AIC              =  22.74025
Log likelihood   = -1012.311079               BIC              = -201.0733
------------------------------------------------------------------------------
   inpatient_cost |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------------+------------------------------------------------------------
probit           |
         overdose |
               1 |   1.860982    .2312691     8.05   0.000     1.407703    2.314261
                 |
        age_final |
               2 |   .4004631    .2831235     1.41   0.157    -.1544488     .955375
               3 |   .5456884    .2957294     1.85   0.065    -.0339306    1.125307
               4 |   .5216619    .3976127     1.31   0.190    -.2576446    1.300968
                 |
           gender |
               2 |   .0373065     .210404     0.18   0.859    -.3750777    .4496907
                 |
        cci_score |   .1427534    .1648231     0.87   0.386     -.180294    .4658008
                 |
       elx_grp_28 |
               1 |   .5560502    .5230124     1.06   0.288    -.4690352    1.581136
                 |
       elx_grp_30 |
               1 |  -.1719662    .7288591    -0.24   0.813    -1.600504    1.256571
                 |
       elx_grp_31 |
               1 |   .0148247    .2859197     0.05   0.959    -.5455677    .5752171
                 |
log_baseline_cost |   .0992009    .0293133     3.38   0.001     .0417479     .156654
            _cons |  -2.471176    .3511603    -7.04   0.000    -3.159438   -1.782914
-----------------+------------------------------------------------------------
glm              |
         overdose |
               1 |  -.3389021    .8647399    -0.39   0.695    -2.033761    1.355957
                 |
        age_final |
               2 |   1.028488    .9636936     1.07   0.286    -.8603167    2.917293
               3 |   1.594489    1.000876     1.59   0.111    -.3671921    3.556169
               4 |   .7234581    1.012998     0.71   0.475    -1.261982    2.708899
                 |
```

```
      gender |
           2 |  -.5251408   .4228238    -1.24   0.214    -1.35386    .3035786
             |
   cci_score |  -.2706861   .1987667    -1.36   0.173    -.6602616   .1188895
             |
  elx_grp_28 |
           1 |  -2.940899   1.592993    -1.85   0.065    -6.063107   .1813089
             |
  elx_grp_30 |
           1 |   .4983783   1.889857     0.26   0.792    -3.205672   4.202429
             |
  elx_grp_31 |
           1 |  -1.112942   .5790143    -1.92   0.055     -2.24779   .0219048
             |
log_baseline_cost |  .1897206   .0620138     3.06   0.002    .0681758    .3112654
       _cons |   8.850585   .8271154    10.70   0.000    7.229468     10.4717
-------------------------------------------------------------------------------
```

Average marginal effects   Number of obs   =   244

Expression   : twopm combined expected values, predict()

dy/dx w.r.t. : 1.overdose


```
-------------------------------------------------------------------------------
             |            Delta-method
             |     dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+-----------------------------------------------------------------
  1.overdose |  17637.84   8227.948     2.14   0.032     1511.354    33764.32
-------------------------------------------------------------------------------
```
Note: dy/dx for factor levels is the discrete change from the base level.

Predictive margins   Number of obs   =   244

Expression   : twopm combined expected values, predict()

```
------------------------------------------------------------------------
             |            Delta-method
             |    Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------
    overdose |
           1 |   23772.66   7020.495     3.39   0.001     10012.75    37532.58
           2 |   6134.829   5609.403     1.09   0.274      -4859.4    17129.06
------------------------------------------------------------------------
```

4. Outpatient costs

```
Iteration 0:   log likelihood = -2274.2017

Iteration 1:   log likelihood = -2208.6055

Iteration 2:   log likelihood = -2207.1545

Iteration 3:   log likelihood = -2207.1535

Iteration 4:   log likelihood = -2207.1535
```

```
Generalized linear models                    No. of obs      =        244

Optimization     : ML                        Residual df     =        233

                                             Scale parameter =   4.235795

Deviance       =   469.236054               (1/df) Deviance =   2.013889

Pearson        =   986.9401244              (1/df) Pearson  =   4.235795


Variance function: V(u) = u^2                [Gamma]

Link function    : g(u) = ln(u)              [Log]


                                             AIC             =   18.18159

Log likelihood   = -2207.153467              BIC             =  -811.6041
```

```
------------------------------------------------------------------------------
                 |                 OIM
 outpatient_cost |    Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------------+------------------------------------------------------------
      1.overdose |   .662436   .2994764    2.21   0.027     .075473    1.249399
                 |
       age_final |
               2 |  .4588781   .4284095    1.07   0.284    -.380789    1.298545
```

```
                 3 |    .7825226    .425233     1.84    0.066    -.0509188    1.615964
                 4 |   -.3093444   .6199111    -0.50    0.618    -1.524348     .905659
                   |
          2.gender |    .4957808   .2829621     1.75    0.080    -.0588147    1.050376
         cci_score |   -.1444597   .2317326    -0.62    0.533    -.5986472    .3097279
       1.elx_grp_28 |   -1.685375   .7473566    -2.26    0.024    -3.150167   -.2205834
       1.elx_grp_30 |    .0399886   .8509749     0.05    0.963    -1.627892    1.707869
       1.elx_grp_31 |   -.7484504    .413254    -1.81    0.070    -1.558413    .0615125
   log_baseline_cost |    .1959248    .035509     5.52    0.000     .1263285    .2655211
             _cons |    6.183886   .4258054    14.52    0.000     5.349323    7.018449
-------------------------------------------------------------------------------
```

.

. margins, dydx(overdose)


```
Average marginal effects                        Number of obs      =        244

Model VCE     : OIM


Expression    : Predicted mean outpatient_cost, predict()

dy/dx w.r.t. : 1.overdose


-------------------------------------------------------------------------------
               |             Delta-method
               |      dy/dx    Std. Err.       z     P>|z|      [95% Conf. Interval]
-------------+-----------------------------------------------------------------
   1.overdose |   2998.982    1491.018     2.01    0.044     76.63937    5921.324
-------------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.
```

.

. margins overdose,

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```
Predictive margins                              Number of obs     =        244

Model VCE     : OIM


Expression    : Predicted mean outpatient_cost, predict()


------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    overdose |
           1 |   6191.048   1390.002     4.45   0.000     3466.694    8915.402
           2 |   3192.066   718.6265     4.44   0.000     1783.584    4600.548
------------------------------------------------------------------------------


.

end of do-file
```

5. Other costs

```
Fitting probit regression for first part:


Iteration 0:   log likelihood = -164.76579

Iteration 1:   log likelihood = -144.46125

Iteration 2:   log likelihood = -144.18529

Iteration 3:   log likelihood = -144.18477

Iteration 4:   log likelihood = -144.18477


Fitting glm regression for second part:


Iteration 0:   log likelihood =  -1425.462

Iteration 1:   log likelihood = -1351.6752

Iteration 2:   log likelihood = -1319.2629

Iteration 3:   log likelihood =  -1318.256

Iteration 4:   log likelihood = -1318.2541

Iteration 5:   log likelihood = -1318.2541


Two-part model

-------------------------------------------------------------------------------
Log pseudolikelihood = -1462.4389          Number of obs   =        244

Part 1: probit
-------------------------------------------------------------------------------
                                           Number of obs   =        244
                                           LR chi2(10)     =      41.16
                                           Prob > chi2     =     0.0000
```

```
Log likelihood = -144.18477                          Pseudo R2       =      0.1249

Part 2: glm
-------------------------------------------------------------------------------

                                             Number of obs   =       145

Deviance        =   422.8296335             (1/df) Deviance =   3.155445

Pearson         =   525.5194005             (1/df) Pearson  =   3.921787


Variance function: V(u) = u^2               [Gamma]

Link function    : g(u) = ln(u)             [Log]


                                             AIC             =   18.33454

Log likelihood   = -1318.254135             BIC             = -244.0527

-------------------------------------------------------------------------------
    others_cost |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
----------------+--------------------------------------------------------------
probit          |
       overdose |
              1 |   .5764128   .1837839     3.14   0.002     .216203    .9366225
                |
      age_final |
              2 |   .6788988   .2437303     2.79   0.005    .2011962   1.156601
              3 |   .4326588   .2587344     1.67   0.094   -.0744512   .9397688
              4 |   .5513308   .3791721     1.45   0.146   -.1918329   1.294494
                |
         gender |
              2 |   .4251966   .1852329     2.30   0.022    .0621467   .7882465
                |
      cci_score |    .308736   .1884878     1.64   0.101   -.0606933   .6781652
                |
     elx_grp_28 |
              1 |   .5154494   .5246035     0.98   0.326   -.5127544   1.543653
                |
     elx_grp_30 |
```

```
           1 |   .0112757    .5538965      0.02   0.984    -1.074342     1.096893
             |
  elx_grp_31 |
           1 |   -.284345    .2471364     -1.15   0.250    -.7687235     .2000334
             |
log_baseline_cost |  .0612936   .0244634      2.51   0.012     .0133462      .109241
       _cons | -1.106196    .2640727     -4.19   0.000    -1.623769    -.5886228
-------------+----------------------------------------------------------------
glm          |
    overdose |
           1 |   1.551324    .4337998      3.58   0.000     .7010919     2.401556
             |
   age_final |
           2 |  -1.443855    .7560193     -1.91   0.056    -2.925625     .037916
           3 |  -1.093934    .7539406     -1.45   0.147     -2.57163     .3837625
           4 |  -1.932791    .8423624     -2.29   0.022    -3.583791    -.2817915
             |
      gender |
           2 |  -.6734859    .4021854     -1.67   0.094    -1.461755     .1147831
             |
   cci_score |   .2540371    .2376598      1.07   0.285    -.2117675     .7198418
             |
  elx_grp_28 |
           1 |  -.9316728    .8627686     -1.08   0.280    -2.622668     .7593225
             |
  elx_grp_30 |
           1 |   .9356786    1.124225      0.83   0.405    -1.267763      3.13912
             |
  elx_grp_31 |
           1 |  -.7913392    .5635196     -1.40   0.160    -1.895817      .313139
             |
log_baseline_cost |  .2806016   .0564755      4.97   0.000     .1699117     .3912915
       _cons |   7.057489    .7917773      8.91   0.000     5.505635     8.609344
-------------+----------------------------------------------------------------
```

```
Average marginal effects                        Number of obs     =        244
```

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```
Expression    : twopm combined expected values, predict()

dy/dx w.r.t. : 1.overdose


--------------------------------------------------------------------------
             |             Delta-method
             |     dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+------------------------------------------------------------
  1.overdose |   12159.03    5836.473    2.08   0.037     719.7569    23598.31
--------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.


Predictive margins                          Number of obs      =        244


Expression    : twopm combined expected values, predict()


--------------------------------------------------------------------------
             |             Delta-method
             |    Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+------------------------------------------------------------
    overdose |
           1 |   14362.62    6026.288    2.38   0.017     2551.312    26173.93
           2 |   2203.586    762.6601    2.89   0.004     708.8001    3698.373
--------------------------------------------------------------------------
```

6. Pharmacy costs

Fitting probit regression for first part:

Iteration 0:   log likelihood = -149.7225

Iteration 1:   log likelihood = -136.06494

Iteration 2:   log likelihood = -135.89186

Iteration 3:   log likelihood = -135.8917

Iteration 4:   log likelihood = -135.8917

Fitting glm regression for second part:

Iteration 0:   log likelihood = -1456.7049

Iteration 1:   log likelihood = -1395.4911

Iteration 2:   log likelihood = -1385.301

Iteration 3:   log likelihood = -1385.2009

Iteration 4:   log likelihood = -1385.2008

Two-part model

Log pseudolikelihood = -1521.0925   Number of obs   =   244

Part 1: probit

                                           Number of obs   =   244
                                           LR chi2(10)   =   27.66
                                           Prob > chi2   =   0.0020

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```
Log likelihood = -135.8917                        Pseudo R2        =     0.0924


Part 2: glm
------------------------------------------------------------------------------

                                                  Number of obs   =       170
Deviance       =   427.8099446                    (1/df) Deviance =  2.690629
Pearson        =   495.1278272                    (1/df) Pearson  =  3.114011

Variance function: V(u) = u^2                     [Gamma]
Link function    : g(u) = ln(u)                   [Log]

                                                  AIC             =  16.42589
Log likelihood   = -1385.20079                    BIC             =  -388.782
------------------------------------------------------------------------------

      phar_cost |     Coef.    Std. Err.      z     P>|z|      [95% Conf. Interval]
----------------+-------------------------------------------------------------
probit          |
       overdose |
             1  |  -.4445152    .1883963    -2.36   0.018    -.8137652    -.0752652
                |
      age_final |
             2  |  -.3735017    .2652341    -1.41   0.159    -.8933511     .1463477
             3  |  -.5122345    .2952557    -1.73   0.083    -1.090925     .0664561
             4  |  -1.104836    .3932684    -2.81   0.005    -1.875628    -.3340439
                |
         gender |
             2  |   .1269393    .1892901     0.67   0.502    -.2440624      .497941
                |
      cci_score |  -.1512138     .123552    -1.22   0.221    -.3933713     .0909437
                |
     elx_grp_28 |
             1  |   .1661636    .6036901     0.28   0.783    -1.017047     1.349374
                |
     elx_grp_30 |
             1  |    .015216    .6256157     0.02   0.981    -1.210968       1.2414
                |
     elx_grp_31 |
```

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```
              1  |   -.0631984    .2564134    -0.25   0.805    -.5657594    .4393626
                 |
log_baseline_cost |    .0965615    .0265668     3.63   0.000     .0444915    .1486315
           _cons |    .6393116    .2609617     2.45   0.014     .1278362    1.150787
-----------------+----------------------------------------------------------------

glm              |
        overdose |
              1  |    .0781905    .3110686     0.25   0.802    -.5314928    .6878739
                 |
       age_final |
              2  |    1.069872    .3800385     2.82   0.005     .3250104    1.814734
              3  |    1.885358    .3999978     4.71   0.000     1.101376    2.669339
              4  |    1.887878     .683738     2.76   0.006     .5477762     3.22798
                 |
          gender |
              2  |   -.9815496    .3215047    -3.05   0.002    -1.611687    -.351412
                 |
       cci_score |    .1338833     .324344     0.41   0.680    -.5018191    .7695858
                 |
       elx_grp_28 |
              1  |   -1.144062    .6982181    -1.64   0.101    -2.512544    .2244205
                 |
       elx_grp_30 |
              1  |   -.1114865    .8150442    -0.14   0.891    -1.708944    1.485971
                 |
       elx_grp_31 |
              1  |   -.8401248     .402763    -2.09   0.037    -1.629526   -.0507238
                 |
log_baseline_cost |     .204456    .0407566     5.02   0.000     .1245745    .2843375
           _cons |    5.429232    .4088537    13.28   0.000     4.627893     6.23057
--------------------------------------------------------------------------------
```

Average marginal effects   Number of obs   =   244

212

```
Expression   : twopm combined expected values, predict()

dy/dx w.r.t. : 1.overdose


------------------------------------------------------------------------
             |            Delta-method
             |      dy/dx   Std. Err.      z    P>|z|    [95% Conf. Interval]
-------------+----------------------------------------------------------
  1.overdose |  -199.0433   556.4555    -0.36   0.721   -1289.676    891.5895
------------------------------------------------------------------------
Note: dy/dx for factor levels is the discrete change from the base level.


Predictive margins                        Number of obs     =        244


Expression   : twopm combined expected values, predict()


------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|    [95% Conf. Interval]
-------------+----------------------------------------------------------
     overdose |
           1 |    1686.81    533.349     3.16   0.002    641.4651    2732.155
           2 |   1885.853   437.9278     4.31   0.000     1027.53    2744.176
------------------------------------------------------------------------


.

end of do-file
```

Vita

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